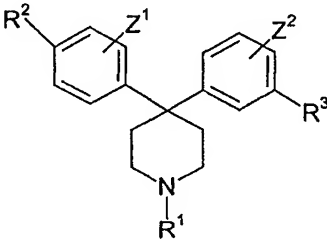




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| (21) International Application Number: PCT/IB99/01512 (22) International Filing Date: 6 September 1999 (06.09.99) (30) Priority Data: 60/099,565 9 September 1998 (09.09.98) US (71) Applicant (for all designated States except US): PFIZER PRODUCTS INC. [US/US]; Eastern Point Road, Groton, CT 06340 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): LIRAS, Spiros [GR/US]; 12 Kidds Way, Stonington, CT 06378 (US). (74) Agents: SPIEGEL, Allen, J. et al.; c/o Simpson, Alison, Urquhart-Dykes & Lord, 91 Wimpole Street, London W1M 8AH (GB). | | (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> |
| (54) Title: 4,4-BIARYLPIPERIDINE DERIVATIVES WITH OPIOID RECEPTOR ACTIVITY <div style="text-align: center;">  </div> <div style="text-align: right;">(I)</div> (57) Abstract <p>The present invention relates to compounds of formula (I), wherein Z¹, Z², R¹, R² and R³ are defined as in the specification, pharmaceutical compositions containing such compounds, the use of such compounds to treat neurological and gastrointestinal disorders.</p> | | |

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4,4-BIARYLPIPERIDINE DERIVATIVES WITH OPIOID RECEPTOR ACTIVITY

Background of the Invention

This invention relates to 4,4-biarylpiperidine derivatives which have utility as ligands for
5 opioid receptors.

In the study of opioid biochemistry, a variety of endogenous opioid compounds and non-endogenous opioid compounds has been identified. In this effort, significant research has been focused on understanding the mechanism of opioid drug action, particularly as it relates to cellular and differentiated tissue opioid receptors.

10 Opioid drugs are typically classified by their binding selectivity in respect of the cellular and differentiated tissue receptors to which a specific drug species binds as a ligand. These receptors include mu (μ), delta (δ) and kappa (κ) receptors.

At least three subtypes of opioid receptors (mu, delta and kappa) are described and documented in the scientific literature. All three receptors are present in the central and
15 peripheral nervous systems of many species including man. Activation of delta receptors produces antinociception in rodents and can induce analgesia in man, in addition to influencing motility of the gastrointestinal tract. (See Burks, T.F. (1995) in "The Pharmacology of Opioid Peptides", edited by Tseng, L.F., Harwood Academic Publishers).

The well known narcotic opiates such as morphine and its analogs are selective for
20 the opioid mu receptor. Mu receptors mediate analgesia, respiratory depression, and inhibition of gastrointestinal transit. Kappa receptors mediate analgesia and sedation.

The existence of the opioid delta receptor is a relatively recent discovery which followed the isolation and characterization of endogenous enkephalin peptides, which are ligands for the delta receptor. Research in the past decade has produced significant
25 information about the delta receptor, but a clear picture of its function has not yet emerged. Delta receptors mediate analgesia, but do not appear to inhibit intestinal transit in the manner characteristic of mu receptors.

U.S. Patent 4,816,586, which issued on March 28, 1989 to P. S. Portoghese, refers to various delta opioid receptor antagonists. These compounds are described as possessing a
30 unique opioid receptor antagonist profile, and include compounds that are highly selective for the delta opioid receptor.

U.S. Patent 4,518,711, which issued May 21, 1985 to V. J. Hruby *et al.*, describes cyclic, conformationally constrained analogs of enkephalins. These compounds include both agonists and antagonists for the delta receptor, and are said to induce pharmacological and
35 therapeutic effects, such as analgesia in the case of agonist species of such compounds. The

antagonist species of the disclosed compounds are suggested to be useful in the treatment of schizophrenia, Alzheimer's disease, and respiratory and cardiovascular functions.

S. Goenechea, *et al*, in "Investigation of the Biotransformation of Meclozine in the Human Body," *J. Clin. Chem. Clin. Biochem.*, 1988, 26(2), 105-15, describe the oral
5 administration of a polyaryl piperazine compound in a study of meclozine metabolization in human subjects.

In "Plasma Levels, Biotransformation and Excretion of Oxatomide in Rats, Dogs, and Man," *Xenobiotica*, 1984, 15(6), 445-62, Meuldermans, W., *et al*. refer to a metabolic study of plasma levels, biotransformation, and excretion of oxatomide.

10 T. Iwamoto, *et al*, in "Effects of KB-2796, A New Calcium Antagonist, and Other Diphenylpiperazines on [³H]nitrendipine Binding", *Jpn. J. Pharmacol.*, 1988, 48(2), 241-7, describe the effect of a polyaryl piperazine as a calcium antagonist.

K. Natsuka, *et al*, in "Synthesis and Structure-Activity Relationships of 1-Substituted 4-(1,2-Diphenylethyl)piperazine Derivatives Having Narcotic Agonist and Antagonist Activity,"
15 *J. Med. Chem.*, 1987, 30 (10), 1779-1787, disclose racemates and enantiomers of 1-substituted 4-[2-(3-hydroxyphenyl)-1-phenylethyl]piperazine derivatives.

European Patent Application No. 458,160, published on November 27, 1991, refers to certain substituted diphenylmethane derivatives as analgesic and antiinflammatory agents, including compounds wherein the methylene bridging group (linking the two phenyl moieties)
20 is substituted on the methylene carbon with a piperidinyl or piperazinyl group.

South African Patent Application No. 8604522, which was published on December 12, 1986, refers to certain N-substituted arylalkyl and aryl-alkylene substituted amino-heterocyclic compounds, including piperidine derivatives, as cardiovascular, antihistamine, and anti-secretory agents.

25 European Patent Application No. 133,323, published on February 20, 1985, refers to certain diphenylmethyl piperazine compounds as non-sedative antihistamines.

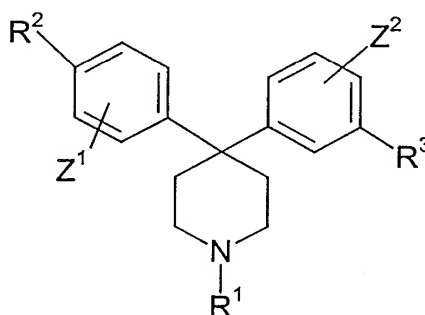
There is a continuing need in the art for improved opioid compounds, particularly compounds which are free of addictive character and other adverse side effects of conventional opiates such as morphine and pethidine.

30 The present inventor has discovered a novel class of 4,4-biaryl piperidine derivatives that are potent and selective delta opioid ligands and are useful for treatment of rejection in organ transplants and skin grafts, epilepsy, chronic pain, neurogenic pain, nonsomatic pain, stroke, cerebral ischemia, shock, head trauma, spinal cord trauma, brain edema, Hodgkin's disease, Sjogren's disease, systemic lupus erythematosus, gastrointestinal disorders such as
35 gastritis, functional bowel disease, irritable bowel syndrome, functional diarrhoea, functional distention, nonulcerogenic dyspepsia and other disorders of motility or secretion, and emesis,

acute pain, chronic pain, neurogenic pain, nonsomatic pain, allergies, respiratory disorders such as asthma, cough and apnea, inflammatory disorders such as rheumatoid arthritis, osteoarthritis, psoriasis and inflammatory bowel disease, urogenital tract disorders such as urinary incontinence, hypoxia (e.g., perinatal hypoxia), hypoglycemic neuronal damage, chemical dependencies and addictions (e.g., a dependency on, or addiction to opiates, benzodiazepines, cocaine, nicotine or ethanol), drug or alcohol withdrawal symptoms, and cerebral deficits subsequent to cardiac bypass surgery and grafting.

Summary of the Invention

This invention relates to compounds of the formula



wherein R¹ is hydrogen, (C₀-C₈)alkoxy-(C₀-C₈)alkyl-, wherein the total number of carbon atoms is eight or less, aryl, aryl-(C₁-C₈)alkyl-, heteroaryl, heteroaryl-(C₁-C₈)alkyl-, heterocyclic, heterocyclic-(C₁-C₈)alkyl, (C₃-C₇)cycloalkyl-, or (C₃-C₇)cycloalkyl-(C₁-C₈)alkyl, wherein said aryl and the aryl moiety of said aryl-(C₁-C₈)alkyl- are selected, independently, from phenyl and naphthyl, and wherein said heteroaryl and the heteroaryl moiety of said heteroaryl-(C₁-C₈)alkyl- are selected, independently, from pyrazinyl, benzofuranyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, isoindolyl, benzimidazolyl, purinyl, carbazolyl, 1,2,5-thiadiazolyl, quinazolinyl, pyridazinyl, pyrazinyl, cinnolyl, phthalazinyl, quinoxalinyl, xanthinyl, hypoxanthinyl, pteridinyl, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, oxazolyl, oxadiazolyl, isoxazolyl, thiazolyl, isothiazolyl, furanyl, pyrazolyl, pyrrolyl, tetrazolyl, triazolyl, thienyl, imidazolyl, pyridinyl, and pyrimidinyl; and wherein said heterocyclic and the heterocyclic moiety of said heterocyclic-(C₁-C₈)alkyl- are selected from saturated or unsaturated nonaromatic monocyclic or bicyclic ring systems, wherein said monocyclic ring systems contain from four to seven ring carbon atoms, from one to three of which may optionally be replaced with O, N or S, and wherein said bicyclic ring systems contain from seven to twelve ring carbon atoms, from one to four of which may optionally be replaced with O, N or S; and wherein any of the aryl, heteroaryl or heterocyclic moieties of R¹ may optionally be substituted with from one to three

substituents, preferably with one or two substituents, independently selected from halo (*i.e.*, chloro, fluoro, bromo or iodo), (C₁-C₆)alkyl optionally substituted with from one to seven (preferably with from zero to four) fluorine atoms, phenyl, benzyl, hydroxy, acetyl, amino, cyano, nitro, (C₁-C₆)alkoxy, (C₁-C₆)alkylamino and [(C₁-C₆)alkyl]₂amino, and wherein any of alkyl
5 moieties in R¹ (*e.g.*, the alkyl moieties of alkyl, alkoxy or alkylamino groups) may optionally be substituted with from one to seven (preferably with from zero to four) fluorine atoms;

R² is hydrogen, aryl, heteroaryl, heterocyclic, SO₂R⁴, COR⁴, CONR⁵R⁶, COOR⁴, or C(OH)R⁵R⁶ wherein each of R⁴, R⁵ and R⁶ is defined, independently, as R¹ is defined above, or R⁵ and R⁶, together with the carbon or nitrogen to which they are both attached, form a
10 three to seven membered saturated ring containing from zero to three heterocarbons selected, independently, from O, N and S, and wherein said aryl, heteroaryl, and heterocyclic are defined as such terms are defined above in the definition of R¹, and wherein any of the aryl, heteroaryl and heterocyclic moieties of R² may optionally be substituted with from one to three substituents, preferably with one or two substituents, independently selected from halo
15 (*i.e.*, chloro, fluoro, bromo or iodo), (C₁-C₆)alkyl optionally substituted with from one to seven (preferably with from zero to four) fluorine atoms, phenyl, benzyl, hydroxy, acetyl, amino, cyano, nitro, (C₁-C₆)alkoxy optionally substituted with from one to seven (preferably with from zero to four) fluorine atoms, (C₁-C₆)alkylamino and [(C₁-C₆)alkyl]₂amino;

R³ is hydroxy, NHSO₂R⁷, C(OH)R⁷R⁸, fluorine or CONHR⁷, wherein R⁷ and R⁸ are the
20 same or different and are selected from hydrogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy and (C₁-C₄)alkoxy-(C₁-C₄)alkyl having a total of 4 or less carbon atoms, and wherein any of the alkyl moieties of R⁷ and R⁸ may optionally be substituted with from one to seven (preferably with from zero to four) fluorine atoms; and

Z¹ and Z² are selected, independently, from hydrogen, halo and (C₁-C₅)alkyl;
25 with the proviso that there are no two adjacent ring oxygen atoms and no ring oxygen atom adjacent to either a ring nitrogen atom or a ring sulfur atom in any of the heterocyclic or heteroaryl moieties of formula I;

and the pharmaceutically acceptable salts of such compounds.

Preferred compounds of the formula I include those wherein R¹ is cyclopropylmethyl,
30 3-cyclohexylpropyl, 2-phenylethyl, 2-methylpentyl, p-methylbenzyl, 2,2,2-trifluoroethyl, or 1-methylpentyl.

Other examples of preferred compounds of the formula I are those wherein R² is diethyl amide, methyl ethyl amide, a diethyl carbinol, tetrazole, or pyrazole.

Other examples of preferred compounds of the formula I are those wherein R³ is
35 hydroxy, fluoro, CONH₂, NHSO₂CH₃, or methoxy.

The compounds of formula I and their pharmaceutically acceptable salts are opioid receptor ligands and are useful in the treatment of a variety of neurological and gastrointestinal disorders. Examples of disorders that can be treated with the compounds of formula I and their pharmaceutically acceptable salts are rejection in organ transplants and skin grafts, epilepsy, chronic pain, neurogenic pain, nonsomatic pain, stroke, cerebral ischemia, shock, head trauma, spinal cord trauma, brain edema, Hodgkin's disease, Sjogren's disease, systemic lupus erythematosus, gastrointestinal disorders such as gastritis, functional bowel disease, irritable bowel syndrome, functional diarrhoea, functional distention, nonulcerogenic dyspepsia and other disorders of motility or secretion, and emesis, acute pain, chronic pain, neurogenic pain, nonsomatic pain, allergies, respiratory disorders such as asthma, cough and apnea, inflammatory disorders such as rheumatoid arthritis, osteoarthritis, psoriasis and inflammatory bowel disease, urogenital tract disorders such as urinary incontinence, hypoxia (e.g., perinatal hypoxia), hypoglycemic neuronal damage, chemical dependencies and addictions (e.g., a dependency on, or addiction to opiates, benzodiazepines, cocaine, nicotine or ethanol), drug or alcohol withdrawal symptoms, and cerebral deficits subsequent to cardiac bypass surgery and grafting.

The present invention also relates to the pharmaceutically acceptable acid addition and base addition salts of compounds of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)]salts. The chemical bases that are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of formula I. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium and magnesium, etc.

The present invention also relates to the pharmaceutically acceptable base addition salts of compounds of the formula I. These salts are all prepared by conventional techniques. The chemical bases that are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of formula I. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium and magnesium, etc.

For a review on pharmaceutically acceptable salts, see Berge et al., J. Pharm. Sci., 66, 1-19 (1977).

This invention also relates to a pharmaceutical composition for treating a disorder or condition, the treatment or prevention of which can be effected or facilitated by modulating (i.e.,
5 increasing or decreasing) binding to opioid receptors in a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically effective salt thereof, that is effective in treating such disorder or condition and a pharmaceutically acceptable carrier.

This invention also relates to a method of treating a disorder or condition, the treatment
10 of which can be effected or facilitated by modulating binding to opioid receptors in a mammal, comprising administering to a mammal in need of such treatment an amount of a compound of the formula I, or a pharmaceutically effective salt thereof, that is effective in treating such disorder or condition.

This invention also relates to a pharmaceutical composition for treating a disorder or
15 condition selected from inflammatory diseases such as arthritis (e.g., rheumatoid arthritis and osteoarthritis), psoriasis, asthma, or inflammatory bowel disease, disorders of respiratory function such as asthma, cough and apnea, allergies, gastrointestinal disorders such as gastritis, functional bowel disease, irritable bowel syndrome, functional diarrhoea, functional distension, functional pain, nonulcerogenic dyspepsia and other disorders of motility or secretion, and
20 emesis, stroke, shock, brain edema, head trauma, spinal cord trauma, cerebral ischemia, cerebral deficits subsequent to cardiac bypass surgery and grafting, urogenital tract disorders such as urinary incontinence, chemical dependencies and addictions (e.g., addictions to or dependencies on alcohol, opiates, benzodiazepines, nicotine, heroin or cocaine), chronic pain, nonsomatic pain, acute pain and neurogenic pain, systemic lupus erythematosus, Hodgkin's
25 disease, Sjogren's disease, epilepsy and rejection in organ transplants and skin grafts in a mammal, including a human, comprising a glutamate neurotransmission modulating effective amount of a compound of the formula I, or a pharmaceutically salt thereof, and a pharmaceutically acceptable carrier.

This invention also relates to a method for treating a condition selected from
30 inflammatory diseases such as arthritis, psoriasis, asthma, or inflammatory bowel disease, disorders of respiratory function such as asthma, cough and apnea, allergies, gastrointestinal disorders such as gastritis, functional bowel disease, irritable bowel syndrome, functional diarrhoea, functional distension, functional pain, nonulcerogenic dyspepsia and other disorders of motility or secretion, and emesis, stroke, shock, brain edema, head trauma, spinal cord
35 trauma, cerebral ischemia, cerebral deficits subsequent to cardiac bypass surgery and grafting, urogenital tract disorders such as urinary incontinence, chemical dependencies and addictions

(e.g., addictions to or dependencies on alcohol, opiates, benzodiazepines, nicotine, heroin or cocaine), chronic pain, nonsomatic pain, acute pain and neurogenic pain, systemic lupus erythematosus, Hodgkin's disease, Sjogren's disease, epilepsy and rejection in organ transplants and skin grafts, in a mammal, comprising administering to such mammal, including a human, an
5 opioid receptor binding modulating effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof.

This invention also relates to a pharmaceutical composition for treating a disorder or condition, the treatment of which can be effected or facilitated by modulating binding to opioid receptors in a mammal, including a human, comprising an opioid receptor binding modulating
10 effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

This invention also relates to a method for treating a disorder or condition, the treatment of which can be effected or facilitated by modulating in a mammal, including a human, comprising administering to such mammal an opioid receptor binding modulating effective
15 amount of a compound of the formula I or a pharmaceutically acceptable salt thereof.

This invention also relates to a method of treating a condition selected from inflammatory diseases such as arthritis, psoriasis, asthma, or inflammatory bowel disease, disorders of respiratory function such as asthma, cough and apnea, allergies, gastrointestinal disorders such as gastritis, functional bowel disease, irritable bowel syndrome, functional
20 diarrhoea, functional distension, functional pain, nonulcerogenic dyspepsia and other disorders of motility or secretion, and emesis, stroke, shock, brain edema, head trauma, spinal cord trauma, cerebral ischemia, cerebral deficits subsequent to cardiac bypass surgery and grafting, urogenital tract disorders such as urinary incontinence, chemical dependencies and addictions (e.g., addictions to or dependencies on alcohol, opiates, benzodiazepines, nicotine, heroin or
25 cocaine), chronic pain, nonsomatic pain, acute pain and neurogenic pain, systemic lupus erythematosus, Hodgkin's disease, Sjogren's disease, epilepsy and rejection in organ transplants and skin grafts in a mammal, comprising administering to a mammal in need of such treatment an amount of a compound of the formula I that is effective in treating such condition.

This invention also relates to a pharmaceutical composition for treating a condition
30 selected from inflammatory diseases such as arthritis, psoriasis, asthma, or inflammatory bowel disease, disorders of respiratory function such as asthma, cough and apnea, allergies, gastrointestinal disorders such as gastritis, functional bowel disease, irritable bowel syndrome, functional diarrhoea, functional distension, functional pain, nonulcerogenic dyspepsia and other disorders of motility or secretion, and emesis, stroke, shock, brain edema, head trauma, spinal
35 cord trauma, cerebral ischemia, cerebral deficits subsequent to cardiac bypass surgery and grafting, urogenital tract disorders such as urinary incontinence, chemical dependencies and

addictions (e.g., addictions to or dependencies on alcohol, opiates, benzodiazepines, nicotine, heroin or cocaine), chronic pain, nonsomatic pain, acute pain and neurogenic pain, systemic lupus erythematosus, Hodgkin's disease, Sjogren's disease, epilepsy and rejection in organ transplants and skin grafts in a mammal, comprising an amount of a compound of the formula I
5 that is effective in treating such condition and a pharmaceutically acceptable carrier.

Unless otherwise indicated, the alkyl groups referred to herein, as well as the alkyl moieties of other groups referred to herein (e.g., alkoxy), may be linear or branched, and they may also be cyclic (e.g., cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl) or be linear or branched and contain cyclic moieties.

10 The term "alkoxy", as used herein, means "-O-alkyl", wherein "alkyl" is defined as above.

The term "alkylene", as used herein, means an alkyl group having two available binding sites (i.e., -alkyl-, wherein alkyl is defined as above).

The term "treating" as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms
15 of such disorder or condition. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

Unless otherwise indicated, "halo" and "halogen", as used herein, refer to fluorine, bromine, chlorine or iodine.

Compounds of the formula I may have chiral centers and therefore may exist in different
20 enantiomeric and diastereomeric forms. This invention relates to all optical isomers and all other stereoisomers of compounds of the formula I, and to all racemic and other mixtures thereof, and to all pharmaceutical compositions and methods of treatment defined above that contain or employ such isomers or mixtures.

Formula I above includes compounds identical to those depicted but for the fact that one
25 or more hydrogen or carbon atoms are replaced by isotopes thereof. Such compounds are useful as research and diagnostic tools in metabolism pharmacokinetic studies and in binding assays. Specific applications in research include radioligand binding assays, autoradiography studies and in vivo binding studies.

Detailed Description of the Invention

30 The compounds of formula I can be prepared according to the methods illustrated in Schemes 1-9 and discussed below. In the reaction schemes and discussion that follow, unless otherwise indicated, Z¹, Z², R¹, R², and R³ and structural formula I are defined as above.

Scheme 1 illustrates a method for the preparation of compounds with the general formula I wherein R³ is (C₁-C₆)alkoxy or fluorine, R² is CONR⁵R⁶ and R¹ is as defined above
35 with the proviso that it is not attached to the piperidine nitrogen at a secondary alkyl carbon or an aryl group. Referring to Scheme 1, a bromobenzene derivative of formula 0, wherein R³ is

methoxy or fluorine, is cooled to -70°C in dry tetrahydrofuran, and then a solution of n-butyllithium is added to it. The resulting solution is then treated with N-benzylpiperidinone and the solution is allowed to warm to room temperature to produce the corresponding compound of formula 1.

5 Alternatively, the benzene derivative of formula 0 in tetrahydrofuran can be treated with magnesium at a temperature from about 0°C to the reflux temperature, preferably starting at room temperature for about three hours and then heating to reflux and letting the reaction proceed for another hour, after which N-benzylpiperidinone is added to the mixture. The resulting solution is then stirred at a temperature ranging from about 0°C to the reflux
10 temperature, preferably at about room temperature, to produce the corresponding compound of formula 1.

 The compound of formula 1, produced by either of the above methods, in dichloroethane is then treated with phenol and aluminum chloride or another Lewis acid (e.g., boron trifluoride etherate), and the resulting solution is stirred at a temperature ranging from
15 about 0°C to the reflux temperature, preferably at about the reflux temperature, to produce the corresponding phenol derivative of formula 2. The compound of formula 2 is then treated with trifluoromethane sulfonic anhydride or another suitable reagent such as N-phenyltrifluoromethanesulfonimide, in the presence of a base such as pyridine, triethylamine, another trialkyl amine, an alkali metal hydride or an alkali metal carbonate, to form the
20 trifluoromethane sulfonate ester of formula 3. This reaction is typically performed in dichloromethane at a temperature ranging from about 0°C to the reflux temperature, preferably at about room temperature.

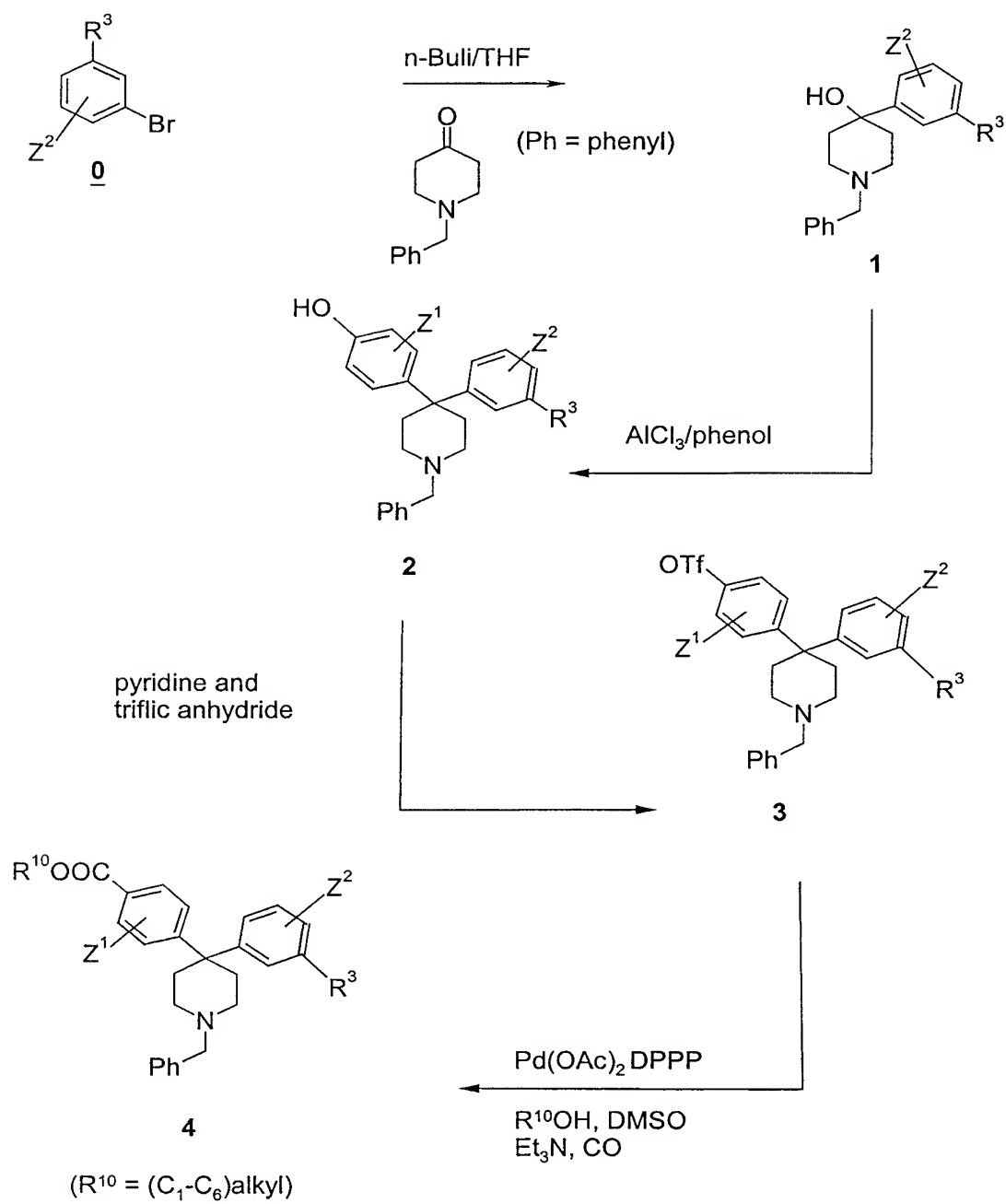
 The compound of formula 3 is placed under a carbon monoxide atmosphere at a pressure ranging from about 14 to 100 psi, in a solution of dimethylsulfoxide and a lower
25 alkanol such as methanol or ethanol, with a suitable trialkylamine base (e.g., triethylamine) and palladium acetate with 1,3-bis(diphenylphosphino)propane (DPPP) or another suitable palladium ligand. Other suitable palladium catalysts such as bis(triphenylphosphine) palladium dichloride may also be used. This reaction is performed at temperatures ranging from about 20°C to 100°C.

30 Treatment of the ester of formula 4 with an aluminum amide of a primary or secondary amine, for example, diethyl amine, in a solvent such as dichloroethane or toluene, at a temperature ranging from about 20°C to about the reflux temperature, preferably at about the reflux temperature, yields the corresponding amide of formula 5. Variations in the nature of the R¹ group on the piperidine nitrogen can be effected in the following manner, as illustrated
35 by process steps (5 → 6 → 7) in Scheme 1. The compound of formula 5 is placed under a

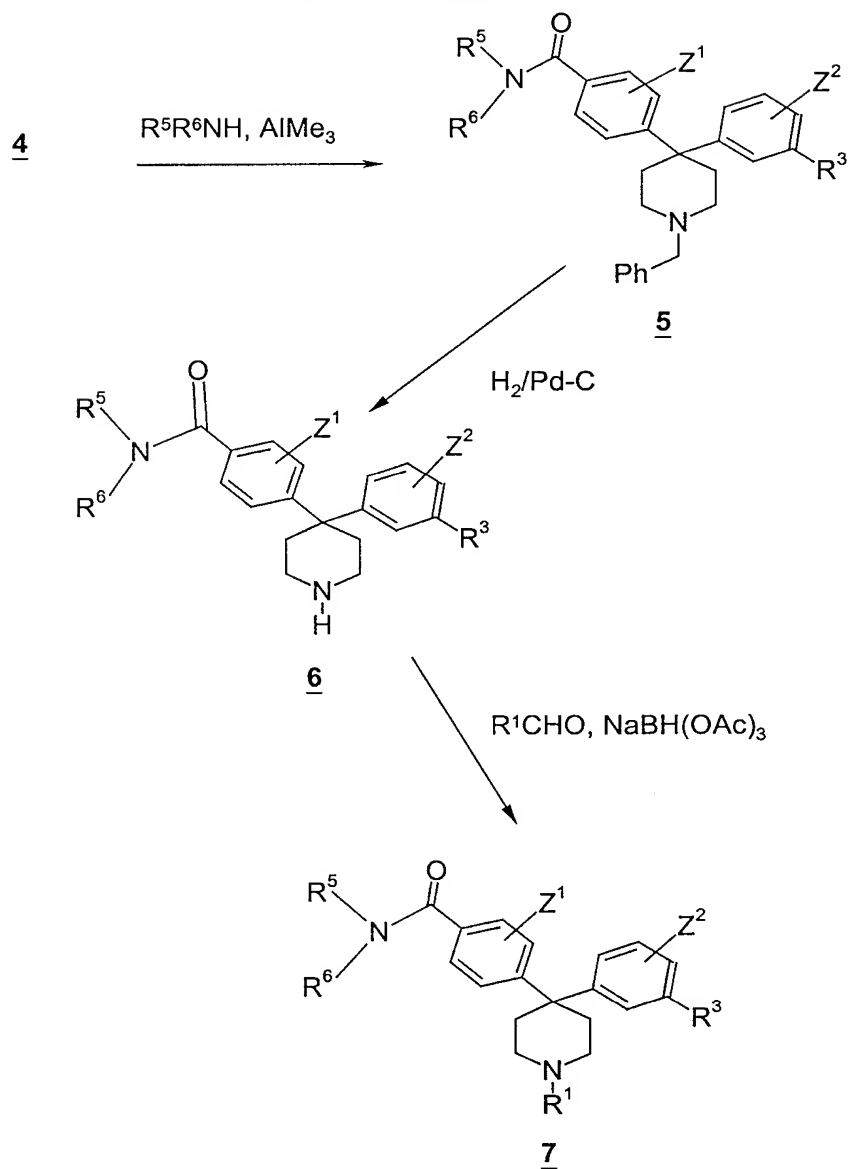
hydrogen atmosphere at pressures ranging from about 14 to 100 psi, in ethanol or other another solvent such as acetic acid or methanol, to produce the corresponding compound of formula 6. This reaction is typically carried out at a temperature from about 0°C to about the reflux temperature, preferably at about room temperature.

- 5 Treatment of the compound of formula 6 with an aldehyde and sodium triacetoxyborohydride or another reducing agent (e.g., sodium borohydride or sodium cyanoborohydride), in dichloromethane, 1,2 dichloroethane or another suitable solvent such as methanol, ethanol or toluene, at a temperature ranging from about 0°C to 100°C, preferably at about room temperature, yields the desired compound of formula 7.

SCHEME 1



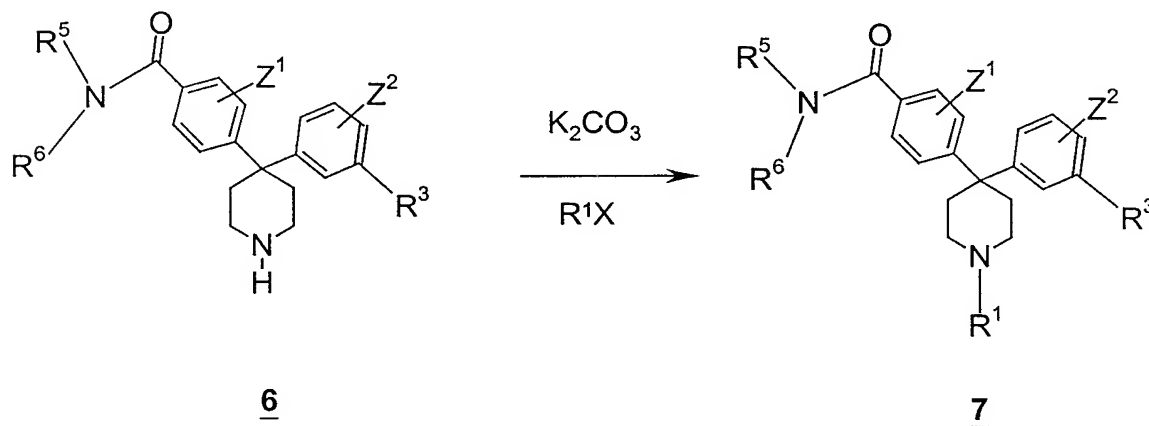
SCHEME 1 CONTINUED



Compounds of formula I wherein R¹ is a group that attaches to the piperidine nitrogen via an aryl moiety or a primary or secondary alkyl moiety, can be prepared by treating the corresponding compound of formula 6 with an alkylating or arylating agent of the formula R¹X, wherein X is a leaving group such as chloro, bromo, iodo, triflate (OTf), mesylate (OMs) or tosylate (Ots), and sodium or potassium carbonate or another alkali metal carbonate or bicarbonate in a solvent such as dimethylformamide, dichloromethane or 1,2 dichloroethane, at a temperature ranging from about 20°C to 100°C, as shown below in Scheme 2.

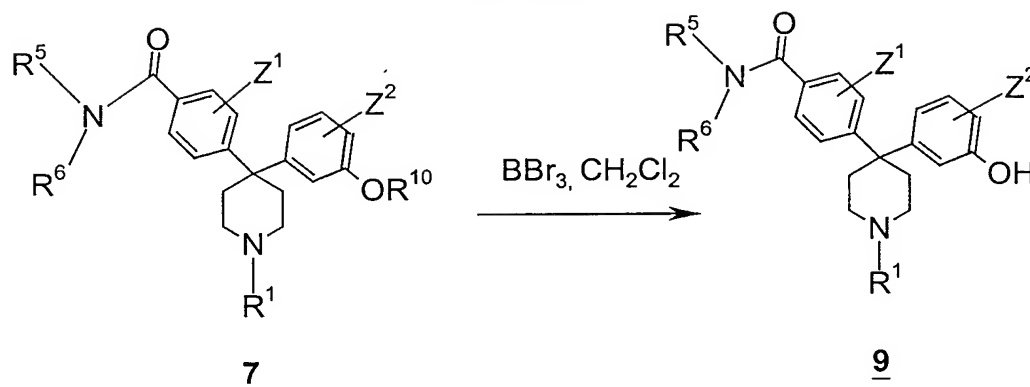
In connection with the definition of formula R¹X in the case where X is an aldehyde moiety (CHO), it is noted that the aldehyde carbon attaches to the piperidine nitrogen and thus R¹ would include an additional carbon atom, which fact is reflected in Example 16 (reactant F → reactant G) where the designation R^xCHO was used.

SCHEME 2



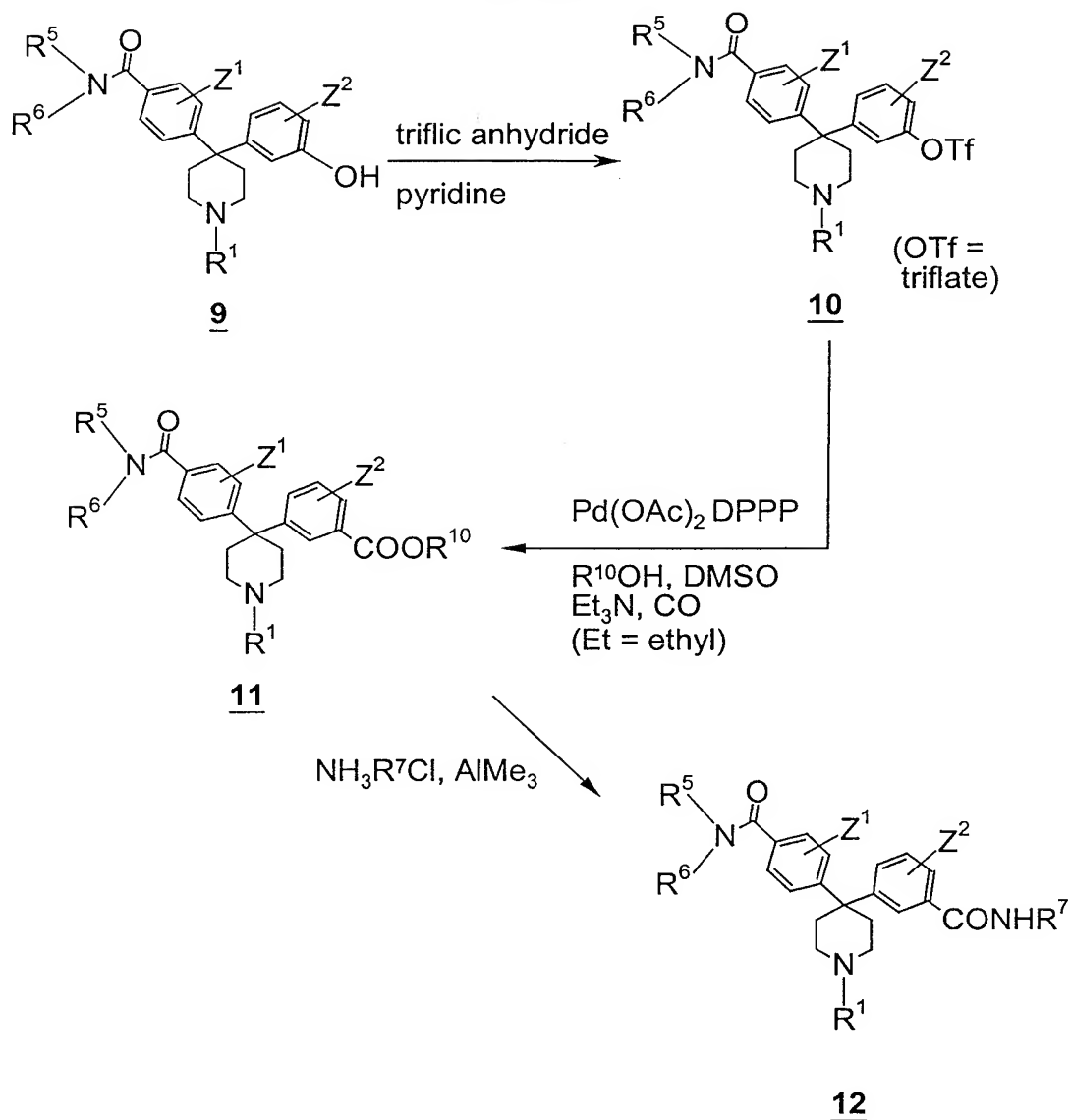
Compounds of the general formula I where R³ is hydroxy can be prepared by deprotecting the corresponding alkyl ether of formula 7 (wherein R¹⁰ is (C₁-C₆)alkyl) with boron tribromide in dichloromethane, or with aqueous hydrobromic acid and acetic acid, or with sodium ethanethiolate in dimethylformamide, at a temperature ranging from about 0°C to the reflux temperature, as shown in Scheme 3. Room temperature is preferred when boron tribromide is used, the reflux temperature is preferred when hydrobromic acid/acetic acid is used, and about 100°C to about 120°C is preferred when sodium ethanemethiolate is used.

SCHEME 3



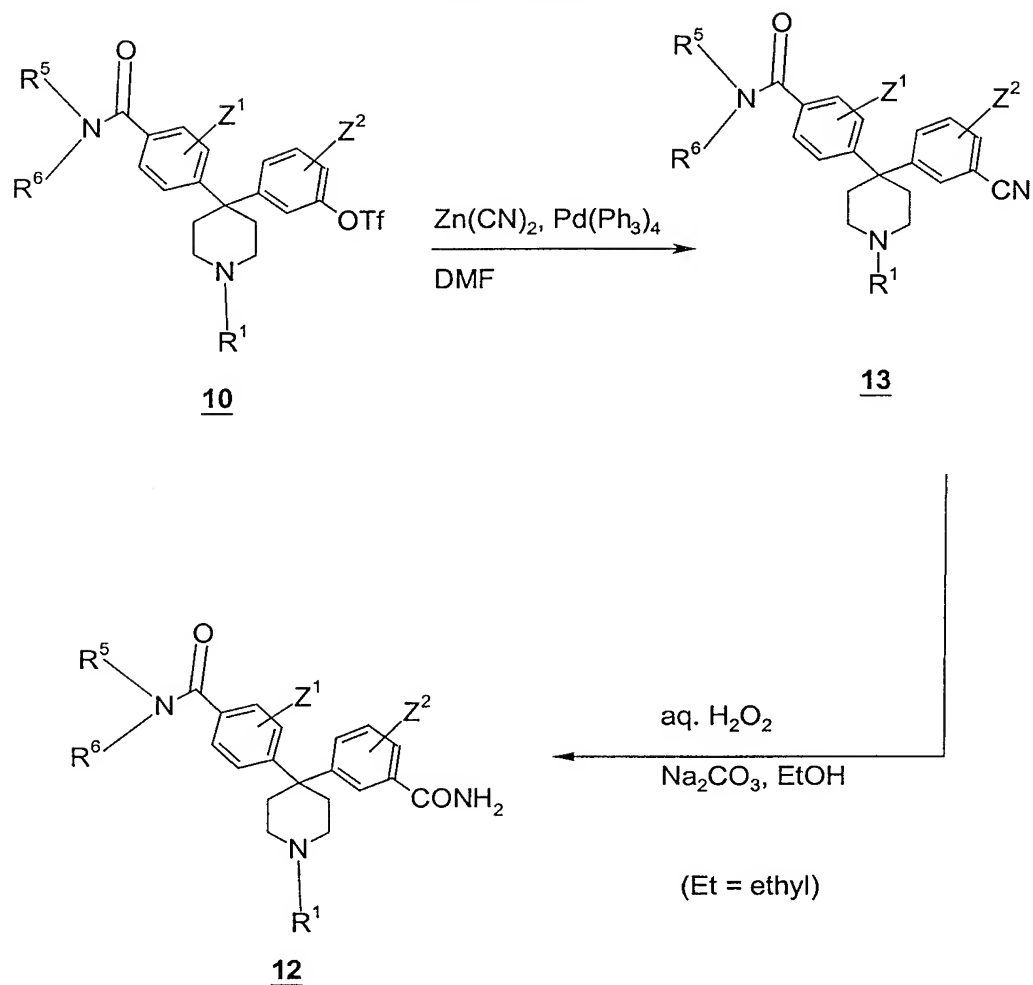
Compounds of the general formula **I** where $\text{R}^3 = \text{CONHR}$ can be prepared from the corresponding phenols of formula **9** as illustrated in Scheme 4 below. This can be accomplished by formation of the triflate of formula **10** using conditions identical to those used for the preparation of compounds of the formula **3** (Scheme 1). The compound of formula **10** is then converted to the corresponding ester of formula **11** using conditions identical to those used in the preparation of esters of the formula **4** (Scheme 1). Treatment of the compound of formula **11** with an aluminum amide of an amine in a solvent such as toluene or 1,2-dichloroethane, at a temperature ranging from about 0°C to about the reflux temperature, preferably at about the reflux temperature, or treatment of the same with a lithium amide in ether or tetrahydrofuran at a temperature ranging from about -78°C to the reflux temperature, preferably at about -78°C , yields the desired compound of formula **I** wherein $\text{R}^3 = \text{CONHR}^4$ and R^4 is (formula **12** below).

SCHEME 4



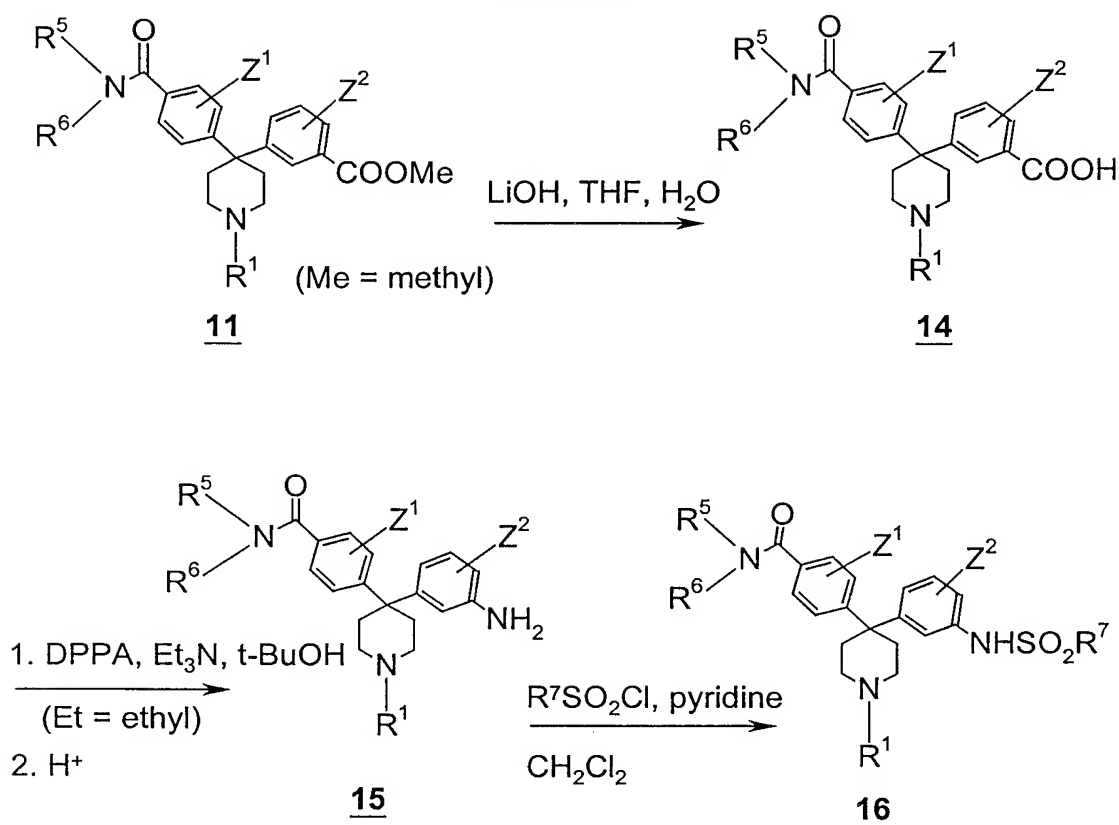
Alternatively, the carboxamide of formula 12 can be accessed by conversion of the triflate ester of formula 10 into the nitrile of formula 13 by treatment with zinc cyanide and a palladium catalyst such as tetrakis triphenylphosphine palladium, in a solvent such as dimethylformamide, or toluene, at a temperature from about 0°C to about the reflux temperature, preferably at about the reflux temperature. The nitrile of formula 13 can be converted into the carboxamide of formula 12 by treatment with hydrogen peroxide and sodium carbonate in ethanol, at a temperature ranging from about 0°C to about the reflux temperature, preferably at about room temperature.

SCHEME 4A



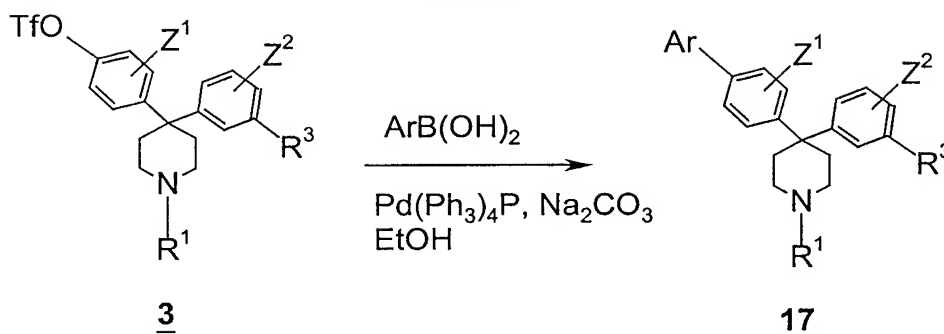
Compounds of the general formula 1 where R³ is NHSO₂R⁵ can be prepared, as illustrated in Scheme 5, by hydrolysis of the ester of formula 11 to the carboxylic acid of formula 14 by reacting it with lithium hydroxide or another alkali metal hydroxide in a mixture of tetrahydrofuran (THF) and water, at a temperature from about room temperature to about the reflux temperature. The compound of formula 14 is then converted into the aniline of formula 15 by reaction with diphenylphosphoryl azide in the presence of triethylamine or another trialkylamine base, in t-butanol at the reflux temperature, followed by acid hydrolysis with aqueous hydrochloric acid in ethyl acetate or with trifluoroacetic acid in methylene chloride. The compound of the formula 15 is then sulfonylated to produce the desired compound of formula 16 with an aryl- or alkylsulfonyl chloride and pyridine triethylamine or another trialkylamine base in dichloromethane, dichloroethane or toluene, at temperatures from about 0°C to about the reflux temperature, preferably at about room temperature.

SCHEME 5



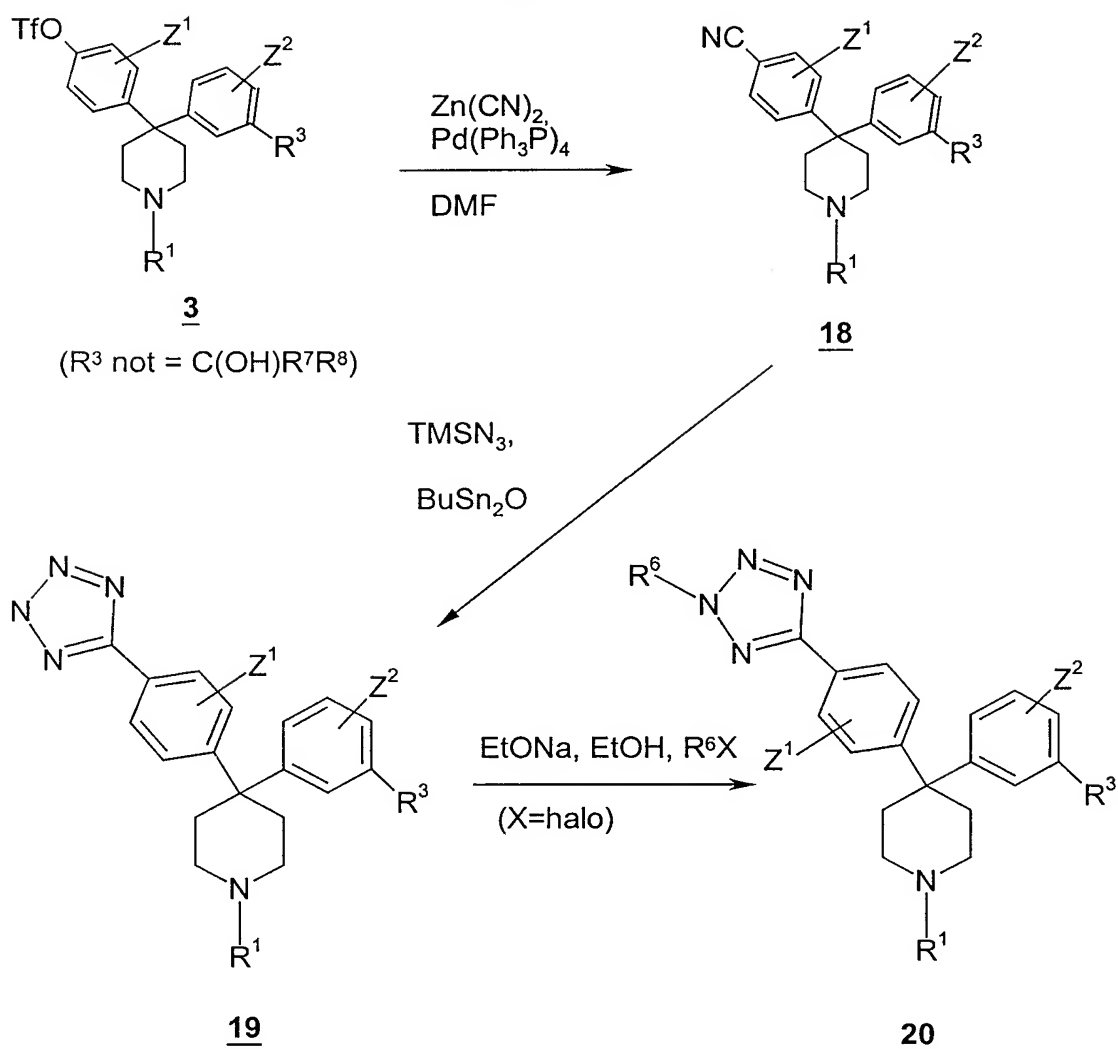
- Compounds of the general formula I wherein R^3 is methoxy, hydroxy or fluorine and R^2 is an aromatic or heteroaromatic moiety (referred to in Scheme 6 as compounds of the
- 5 formula 17) can be prepared by organometallic coupling of a compound of the formula 3 with an aryl and heteroaryl boronic acid, wherein aryl and heteroaryl are defined as in the definitions of R^1 and R^2 , in a solvent such as ethanol or toluene, in the presence of a of palladium catalyst such as tetrakis triphenylphosphine palladium and a trialkylamine base (e.g., triethylamine) or alkali metal carbonate base, as shown below in Scheme 6. This
- 10 reaction is generally carried out at a temperature from about room temperature to about the reflux temperature, preferably at about the reflux temperature.

SCHEME 6



Compounds of the formula 1 wherein R^2 is tetrazoyl can be prepared, as illustrated in Scheme 7 below, by conversion of the appropriate triflate of formula 3 into the corresponding nitrile of formula 18. This can be accomplished by reacting the triflate compound with zinc cyanide and a palladium catalyst such as tetrakis triphenylphosphine palladium in a solvent such as dimethylformamide, at a temperature ranging from about 0°C to about 100°C, preferably at about the reflux temperature. The formation of the tetrazole proceeds by treatment of the resulting nitrile with sodium or trimethylsilylazide and a catalytic amount of tin oxide in a solvent such as dimethylformamide, preferably at about the reflux temperature or toluene, at a temperature ranging from about 20°C to about the reflux temperature. Alkylation of the tetrazole proceeds by reaction with triethylamine or another trialkylamine base or an alkali metal hydride, alkoxide or carbonate, and with the appropriate compound of the formula R^6X wherein X is a leaving group such as chloro, bromo, iodo, triflate, mesylate or tosylate, in a solvent such as methanol, ethanol, or tetrahydrofuran, at temperatures ranging from about 0°C to about the reflux temperature, preferably at about room temperature.

SCHEME 7

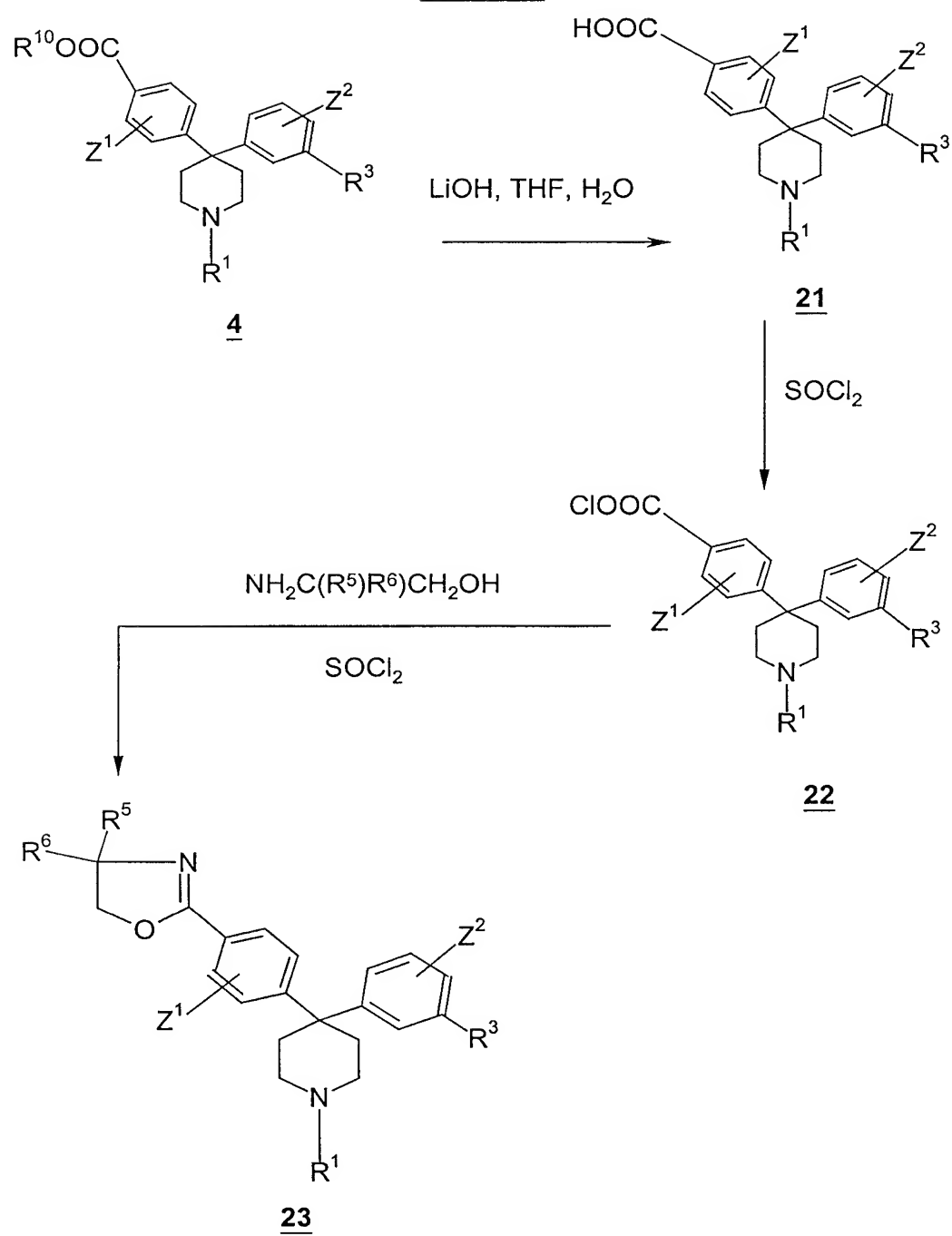


- Compounds of the general formula **I** wherein R^3 is fluoro or methoxy and R^2 is a heterocycle such as oxazoline or thiazoline can be prepared, as illustrated in Scheme 8, from the appropriate carboxylic acid of formula **20**, which can be prepared using conditions identical to those used for the formation of the carboxylic acids of formula **12** (Scheme 5). The carboxylic acid of formula **20** is first converted into the corresponding acid chloride by reaction with oxalyl chloride or thionyl chloride and then treated with the appropriate amino alcohol of the formula $\text{NH}_2\text{C(R}^5\text{)(R}^6\text{)CH}_2\text{OH}$ or amino thiol of formula $\text{NH}_2\text{C(R}^5\text{)(R}^6\text{)CH}_2\text{S}$.
- Conversion to the acid chloride is generally carried out neat or in a solvent such as dichloromethane or dichloroethane, at a temperature from about 0°C to about the reflux temperature, preferably at about the reflux temperature. Treatment with the appropriate amino alcohol or amino thiol is generally carried out at similar temperatures in a solvent such

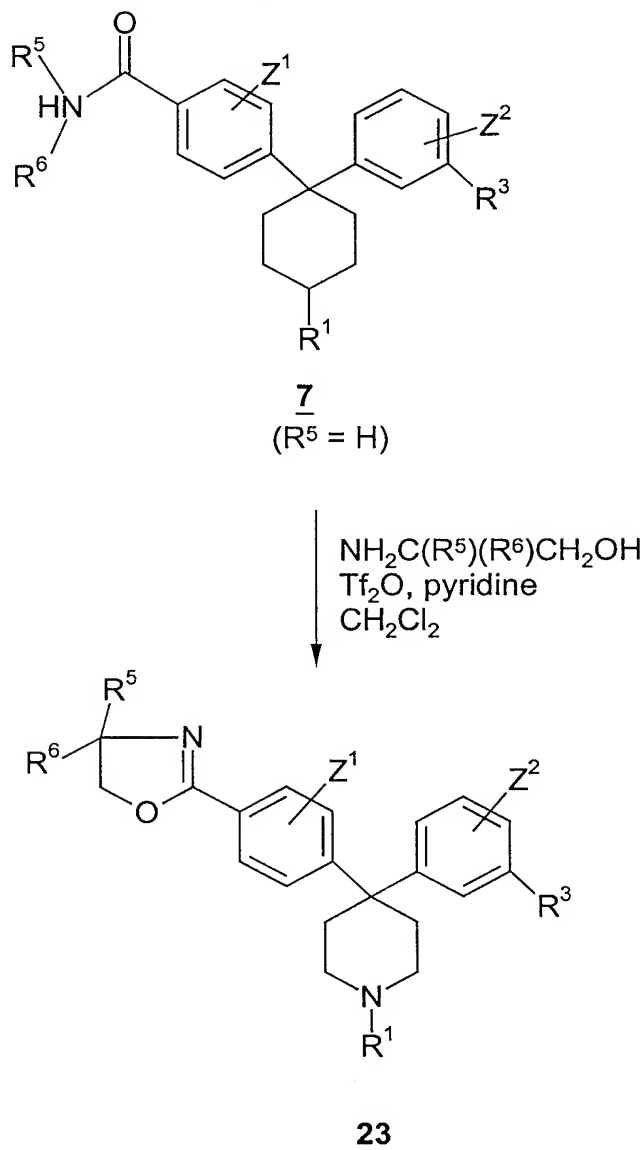
as dichloromethane or dichloroethane. Dehydrative cyclization using thionyl chloride, neat or in dichloromethane about the reflux temperature, or using trifluoromethane sulfonic anhydride and pyridine or a trialkyl amine such as triethylamine, in dichloromethane, dichloroethane or tetrahydrofuran, at a temperature ranging from about -78°C to about the reflux temperature, preferably starting at about -78°C and gradually warming to room temperature, yields the desired compound of formula I. This series of reactions is illustrated in Scheme 8 for the preparation of compounds of the formula I wherein R³ is fluoro or methoxy and R² is 4,4-dimethyloxazolyl (formula 23 in Scheme 8).

Alternatively, compounds of the formula 23 can be prepared, as illustrated in Scheme 8A, by treatment of the appropriate amide of formula 7 (Scheme 1) with triflic anhydride, pyridine or a trialkylamine base such as triethylamine, and the appropriate amino alcohol or amino thiol, as referred to in the preceding paragraph, in a solvent such as dichloromethane or dichloroethane, at a temperature from about -78°C to about room temperature, preferably starting at -78°C and slowly allowing the reaction mixture to warm to room temperature.

SCHEME 8

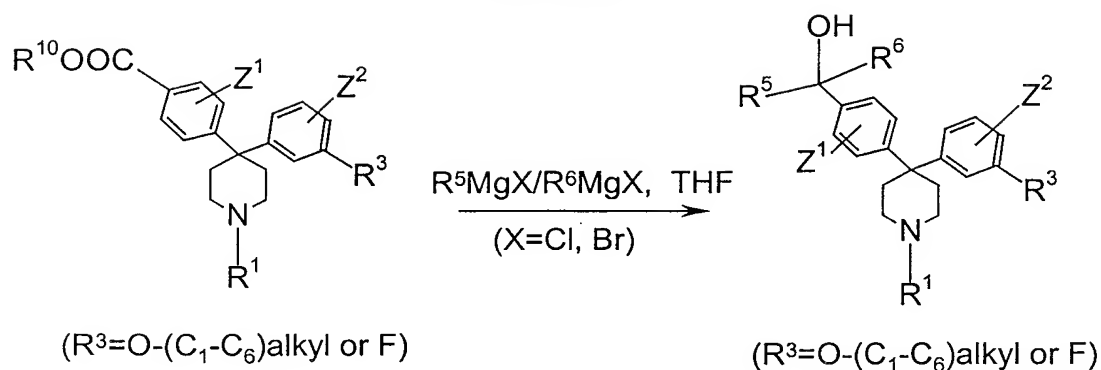


SCHEME 8A



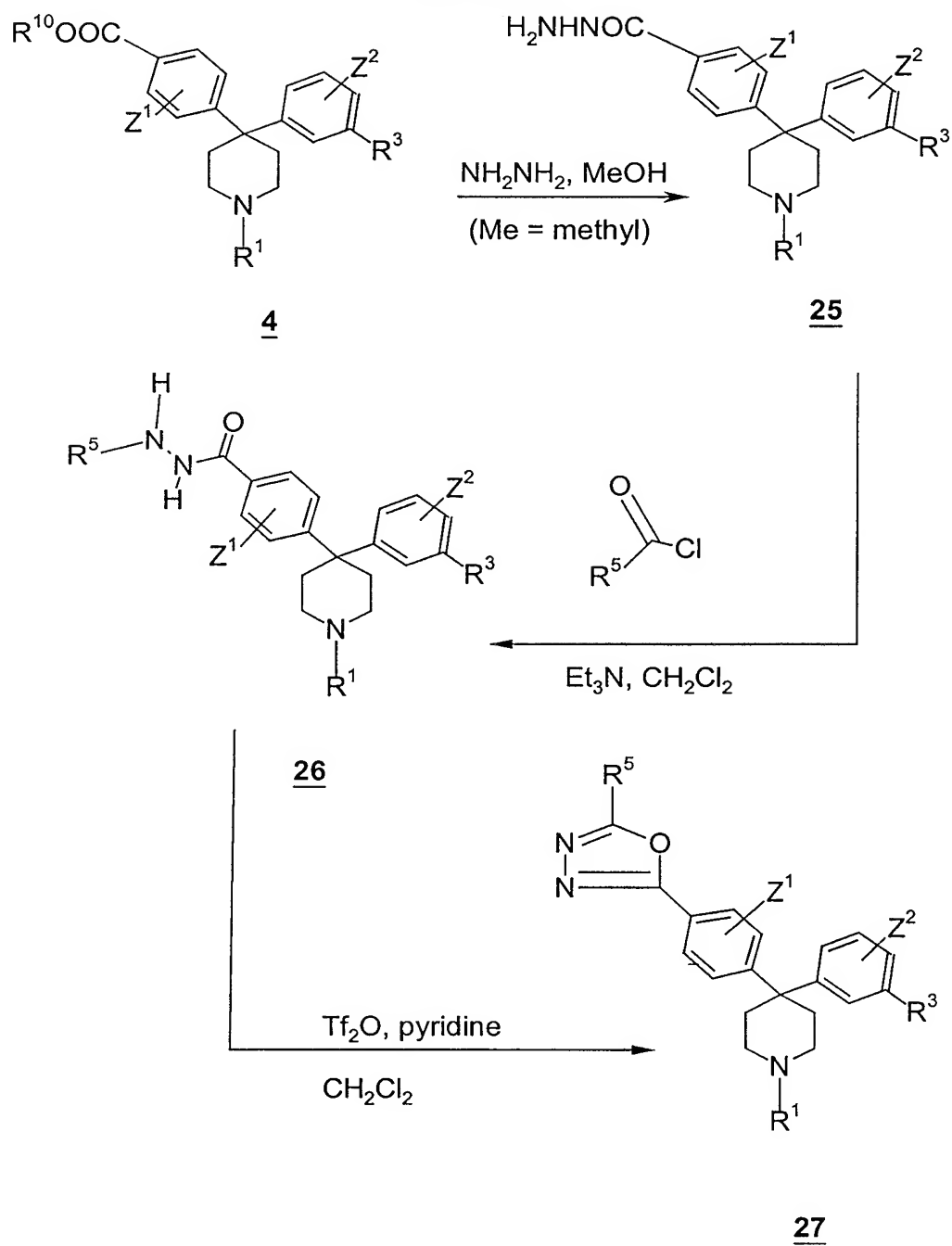
Compounds of the general formula **1** where R³ is fluoro or methoxy and R² is a carbinol such as diethyl carbinol (referred to in Scheme 9 as compounds of the formula **24**) can be prepared, as illustrated in Scheme 9, by treatment of the ester of formula **4** with an alkyl Grignard or alkyl lithium reagent, in a solvent such as ether or tetrahydrofuran, at a temperature ranging from about -78°C to about the reflux temperature, preferably starting at room temperature and heating to about the reflux temperature.

SCHEME 9

**4****24**

Compounds of the general formula **I** where R^2 is a diazaoxazole ring (e.g., compounds of the formula **27** in Scheme 10) can be prepared, as illustrated in Scheme 10, by treatment of the methyl ester of formula **4** with hydrazine hydrate in methanol, at a temperature from about 0°C to about the reflux temperature, preferably at about the reflux temperature, to form the hydrazide of formula **25**. Subsequent acylation with an acid chloride and pyridine, triethylamine or another trialkylamine in a solvent such as dichloromethane, dichloroethane or toluene, at a temperature from about 0°C to about the reflux temperature, preferably at about room temperature provides the corresponding compound of formula **26**. Cyclization can be accomplished using a reagent combination such as triphenylphosphine/iodine and triethylamine or another trialkylamine in a solvent such as tetrahydrofuran, or toluene, at a temperature from about 0°C to about the reflux temperature, preferably at about room temperature or using triflic anhydride and pyridine or a trialkylamine in dichloromethane, or tetrahydrofuran, at a temperature from about -78°C to about room temperature, preferably starting at -78°C and gradually warming to room temperature, or using thionyl chloride in dichloromethane, or neat, at a temperature from about room temperature to about the reflux temperature, preferably at about the reflux temperature, to yield the desired compound of formula **27**.

SCHEME 10



The preferred method of making compounds of the formula I wherein R^3 is OH, $NHSO_2R^7$, $C(OH)R^7R^8$ or $C(=O)NHR^7$ is to make the analogous compounds wherein R^3 is O- (C_1-C_6) alkyl and then derivatize them using standards methods well known in art and illustrated in the foregoing schemes.

5 The starting materials used in the processes of Schemes 1-10 are either commercially available, known in the literature, or readily obtainable from commercially available or known compounds using methods that are well known in the art or described above.

 Unless indicated otherwise, the pressure of each of the above reactions is not critical.
10 Generally, the reactions will be conducted at a pressure from about one to about three atmospheres, preferably at ambient pressure (about one atmosphere).

 The preparation of other compounds of the formula I not specifically described in the foregoing experimental section can be accomplished using combinations of the reactions described above that will be apparent to those skilled in the art.

15 The compounds of the formula I that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. The acid that can be used to prepare the pharmaceutically acceptable acid addition salts of the base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as hydrochloride, hydrobromide, hydroiodide, nitrate,
20 sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the formula I from the reaction mixture as a pharmaceutically
25 unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent, and subsequently convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic
30 solvent such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is obtained.

 Compounds of the formula that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. These salts are all prepared by conventional techniques. The chemical bases that are used as reagents to prepare the pharmaceutically
35 acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of formula I. Such non-toxic base salts include those derived from such

pharmacologically acceptable cations as sodium, potassium, calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

The compounds of the formula I and the pharmaceutically acceptable salts thereof (hereinafter, also referred to, collectively, as "the active compounds of the invention") are useful for the treatment of neurodegenerative, psychotropic and drug or alcohol induced deficits and are potent opioid receptor ligands. The active compounds of the invention may therefore be used in the treatment of disorders and conditions, such as those enumerated above, that can be treated by modulating binding to an opioid receptor.

The ability of the compounds of formula I to bind to the various opioid receptors and their functional activity at such receptors can be determined as described below. Binding to the delta opioid receptor can be determined using procedures well known in the art, such as those referred to by Lei Fang *et al.*, *J. Pharm. Exp. Ther.*, **268**, 1994, 836 - 846 and Contreras *et al.*, *Brain Research*, **604**, 1993, 160 - 164.

In the description of binding and functional assays that follows, the following abbreviations and terminology are used.

DAMGO is [D-Ala²,N-MePhe⁴,Gly⁵-ol]enkephalin).

U69593 is ((5a, 7a, 8b)-(+)-N-methyl-N-(7-[1-pyrrolidinyl]-1-oxasipropyl)-4,5-dec-8-yl)-benzeneacetamide).

SNC-80 is (+)-4-[(α R)- α [(2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl]-3-methoxybenzyl]-N,N-diethylbenzamide.

nor BNI is nor-binaltorphimine.

CTOP is 1,2-Dithia-5,8,11,14,17-pentazacycloeicosane, cyclic peptide derivative

DPDPE is [D-enkephalin, D-Pen⁵]enkephalin).

[³H]-DAMGO, [³H]-U69593, norBNI, and CTOP are all commercially available from DuPont, Amersham International, RBI and DuPont, Amersham International, RBI and DuPont respectively.

[³H]-SNC80 was prepared by Amersham International.

Opioid (μ and κ) receptor binding assays can be performed in guinea-pig brain membrane preparations. Binding assays can be carried out at 25°C for 60 minutes in 50 mM

Tris (pH 7.4) buffer. [^3H]-DAMGO (2 nM) and [^3H]-U-69,593 (2 nM) can be used to label mu and kappa receptor binding sites, respectively. The protein concentration can be approximately 200 $\mu\text{g}/\text{well}$. Non-specific binding can be defined with 10 μM naloxone.

Delta receptor binding assays can be performed in a stable line of CHO cells
5 expressing the human delta receptor. The binding assay can be carried out at 25°C for 120 minutes in 50 mM Tris (pH 7.4) buffer. [^3H]-SNC-80 can be used to label delta receptor binding sites. The protein concentration can be approximately 12.5 $\mu\text{g}/\text{well}$. Non-specific binding can be defined with 10 μM naltrexone.

The binding reaction can be terminated by rapid filtration through glass fibre filters,
10 and the samples can be washed with ice-cold 50 mM Tris buffer (pH 7.4).

Agonist activity at the delta, mu and kappa opioid receptors can be determined as follows.

Opioid (delta, mu and kappa) activity is studied, as described below, in two isolated tissues, the mouse deferens (MVD)(δ) and the guinea-pig myentric plexus with attached
15 longitudinal muscle (GPMP) (μ and κ).

MVD (DC1 strain, Charles River, 25-35 g) are suspended in 15 ml organ baths containing Mg^{++} free Krebs' buffer of the following composition (mM): NaCl, 119; KCl, 4.7; NaHCO_3 , 25; KH_2PO_4 , 1.2; CaCl_2 , 2.5 and glucose, 11. The buffer is gassed with 95% O_2 and 5% CO_2 . The tissues are suspended between platinum electrodes, attached to an isometric
20 transducer with 500 mg tension and stimulated with 0.03 Hz pulses of 1-msec pulse-width at supramaximal voltage. IC_{50} values are determined by the regression analysis of concentration-response curves for inhibition of electrically-induced contractions in the presence of 300 nM of the mu-selective antagonist CTOP. This test is a measure of δ agonism.

25 Guinea-pig (Porcellus strain, male, 450-500 g, Dunkin Hartley) myentric plexus with attached longitudinal muscle segments are suspended with 1 g of tension in Krebs' buffer and stimulated with 0.1 Hz pulses of 1-msec pulse-width at supramaximal voltage. Mu functional activity is determined in the presence of 10 nM nor-BNI with 1 μM of the mu selective agonist, DAMGO, added to the bath at the end of the experiment to define a maximal response. This
30 test is a measure of mu agonism.

Kappa functional activity is determined in the presence of and 1 μM CTOP with 1 μM of the kappa selective agonist U-69,593 added at the end of the experiment to define a maximal response. All inhibitions of twitch height for test compounds are expressed as a percentage of the inhibition obtained with the standard agonist and the corresponding IC_{50}
35 values determined.

The following procedure can be used to determine the activity of the therapeutic agents of this invention as agonists and as antagonists of delta opioid receptors.

Cell Culture: Chinese hamster ovary cells expressing the human delta opioid receptor are passaged twice weekly in Hamis F-12 media with L-glutamine containing 10% fetal bovine serum and 450 µg/mL hygromycin. Cells are prepared for assays 3 days prior to the experiment. 15 mL of 0.05% trypsin/EDTA is added to a confluent triple flask, swirled and decanted to rinse. 15 mL of 0.05% trypsin/EDTA is again added, and the flask is placed into a 37C incubator for 2 minutes. Cells are removed from the flask by banking, and supernatant poured off into a 50 mL tube. 30 mL of media is then added to the flask to stop the action of the trypsin, and then decanted into the 50 mL tube. Tube is then centrifuged for 5 minutes at 1000 rpm, media decanted, and the pellet resuspended into 10 mL of media. Viability of the cells is assessed using trypan blue, the cells counted and plated out into 96 well poly-D-lysine coated plates at a density of 7,500 cells/well.

Antagonist Test Plate: Cells plated 3 days prior to assay are rinsed twice with PBS. The plates are placed into a 37C water bath. 50 µL of assay buffer (PBS, dextrose 1 mg/mL, 5mM MgCl₂, 30 mM HEPES, 66.7 µg/mL of IBMX) is then added to designated wells. Fifty microliters of appropriate drug is then added to designated wells, and timed for 1 minute. Fifty microliters of 10 µM forskolin + 0.4nM DPDPE (final assay concentration is 5 µM forskolin, 0.2nM DPDPE) is then added to appropriate wells, and timed for 15 minutes. The reaction is stopped by the addition of 10 µL of 6N perchloric acid to all wells. To neutralize, 13 µL of 5N KOH is added to all wells, and to stabilize 12 µL of 2M Tris, pH 7.4 is added to all wells. Mix by shaking on an orbital shaker for 10 minutes, and centrifuge at setting 7 for 10 minutes. Aliquot into 3H plate.

Agonist Test Plate: Cells plated 3 days prior to assay are rinsed twice with PBS. The plates are placed into a 37°C water bath. Fifty microliters of assay buffer (PBS, dextrose 1 mg/mL, 5mM MgCl₂, 30mM HEPES, 66.7 µg/mL of IBMX) is then added to designated wells. Fifty microliters of appropriate drug + 10 µM forskolin (final assay concentration is 5µM forskolin) is then added to all wells, and timed for 15 minutes. The reaction is then stopped by the addition of 10 µL of 6N perchloric acid to all wells. To neutralize, 13 µ of 5N KOH is added to all wells, and to stabilize 12 µL of 2M Tris, pH 7.4 is added to all wells. Mix by shaking on an orbital shaker for 10 minutes, and centrifuge at setting 7 for 10 minutes. Aliquot into 3H plate.

Both test plates are placed into an Amersham 3H cAMP binding kit overnight, and harvested onto GF/B filters previously soaked in 0.5% PEI with a Skatron using 50 mM Tris HCl pH 7.4 at 4°C. Filtermats can be air-dried overnight then place in bags with 20 ml

Betaplate scintillation cocktail and counted on a Betaplate counter for 60 sec per sample. Data can be analyzed using Excel.

The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of the invention may be formulated for oral, buccal, transdermal (e.g., patch), intranasal, parenteral (e.g., intravenous, intramuscular or subcutaneous) or rectal administration or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycollate); or wetting agents (e.g., sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters or ethyl alcohol); and preservatives (e.g., methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation

from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

In general, a therapeutically effective daily oral or intravenous dose of the compounds of formula (I) and their salts is likely to range from 0.001 to 50 mg/kg body weight of the subject to be treated, preferably 0.1 to 20 mg/kg. The compounds of the formula (I) and their salts may also be administered by intravenous infusion, at a dose which is likely to range from 0.001-10 mg/kg/hr.

Tables or capsules of the compounds may be administered singly or two or more at a time as appropriate. It is also possible to administer the compounds in sustained release formulations.

The physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Alternatively, the compounds of the formula (I) can be administered by inhalation or in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. An alternative means of transdermal administration is by use of a skin patch. For example, they can be incorporated into a cream consisting of an aqueous emulsion of polyethylene glycols or liquid paraffin. They can also be incorporated, at a concentration of between 1 and 10% by weight, into an ointment consisting of a white wax or white soft paraffin base together with such stabilisers and preservatives as may be required.

The following Examples illustrate the preparation of the compounds of the present invention. Commercial reagents were utilized without further purification. All NMR data were recorded at 250, 300 or 400 MHz in deuteriochloroform unless otherwise specified and are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent. All non-aqueous reactions were carried out in dry glassware with dry solvents under an inert atmosphere for convenience and to maximize yields. All reactions were stirred with a magnetic stirring bar unless otherwise stated. Unless otherwise stated, all mass spectra were obtained using chemical impact conditions. Ambient or room temperature refers to 20-25°C.

EXAMPLE 1**N,N-DIETHYL-4-[4-(3-HYDROXY-PHENYL)-PIPERIDIN-4-YL]-BENZAMIDE****A. 1-Benzyl-4-(3-methoxy-phenyl)-piperidin-4-ol**

To a solution of 3-bromoanisole (20.9 mL, 0.16 mmol) in THF (150 mL) at -78°C under a nitrogen atmosphere was added n-BuLi (66 mL, 0.16 mmol, 2.5M in hexanes) over 10 min. The resulting slurry was stirred at -78°C for 1 hour. To the mixture was added a solution of N-benzyl-4-piperidinone (27.8 mL, 0.15 mmol) in THF (30 mL). The reaction was stirred at -78°C for 2 hours and at room temperature for 10 hours. The mixture was poured slowly over ice-water (100 mL) and the aqueous layer was washed with EtOAc (3 x 50 mL). The combined organic extracts were dried (MgSO₄) and concentrated. The crude residue was purified by flash chromatography with hexanes/EtOAc (3:1) to afford 42.2 g of the alcohol (95% yield). ¹HNMR (400 MHz, CDCl₃) δ 7.35-7.22 (comp, 6H), 7.07-7.04 (comp, 2H), 6.80-6.77 (m, 1H), 3.80 (s, 1H), 3.58 (s, 1H), 2.79 (d, 2H), 2.48 (t, 2H), 2.19-2.13 (comp, 2H), 1.72 (dd, 2H), 1.58 (s, 1H); MS (M+1) 298.3.

B. 4-[1-Benzyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-phenol

To a solution of 1-Benzyl-4-(3-methoxy-phenyl)-piperidin-4-ol (21.7g, 73.1 mmol) in (CH₂)₂Cl₂ (200 mL) was added phenol (20.7 g, 220 mmol) followed by portionwise addition (highly exothermic) of AlCl₃ (29.3 g, 200 mmol). The reaction mixture was heated to reflux for 10 hours. The mixture was cooled to room temperature and was slowly poured into a mixture of crushed ice (50 mL) and 30 % aq. NH₄OH (120 mL). The mixture was stirred vigorously for 20 minutes and was then filtered through celite. The celite cake was washed with CH₂Cl₂ (200 mL). The organic layer was separated and the aqueous layer was washed with CH₂Cl₂ (3 x 100 mL). The combined organic layers were dried (MgSO₄) and concentrated. The crude residue was purified by flash chromatography with hexanes/EtOAc (1:1) to afford 20.1 g (73 % yield) of 4-[1-Benzyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-phenol. ¹HNMR (400 MHz, CD₃OD) δ 7.28-7.20 (comp, 5H), 7.14 (t, 1H), 7.07 (d, 2H), 6.83 (d, 2H), 6.76 (s, 1H), 6.70-6.60 (comp, 3H), 3.69 (s, 3H), 3.39 (s, 2H), 2.50-2.40 (comp, 4H), 2.39-2.29 (comp, 4H); MS (M+1) 374.2.

C. Trifluoro-methanesulfonic acid 4-[1-benzyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-phenyl ester

To a slurry of 4-[1-Benzyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-phenol (22.3 g, 59.8mmol) in CH₂Cl₂ (200 mL) at 0°C was added pyridine (9.26 mL, 89.7 mmol) followed by dropwise addition of triflic anhydride (15.1 mL, 89.7 mmol) over 10 minutes. The reaction mixture was stirred at 0°C for 1 hour and at room temperature for 2 hour. The solution was then cooled to 0°C and 40 mL of cold saturated aqueous NaHCO₃ were added. The organic layer was separated and the aqueous layer was washed with CH₂Cl₂ (3 x 50 mL). The

combined organic layers were dried (MgSO_4) and concentrated. The crude residue was purified by flash chromatography with hexanes/EtOAc (3:1) to afford 22.1 g (75 % yield) of trifluoro-methanesulfonic acid 4-[1-benzyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-phenyl ester. $^1\text{HNMR}$ (400 MHz, CDCl_3) δ 7.32-7.20 (comp, 8H), 7.14 (d, 2H), 6.84 (d, 1H), 6.81 (s, 1H), 6.72 (dd, 1H), 3.77 (s, 3H), 3.41 (s, 2H), 2.55-2.38 (comp, 8H); MS (M+1) 505.9.

D. 4-[1-Benzyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-benzoic acid methyl ester

To a solution of trifluoro-methanesulfonic acid 4-[1-benzyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-phenyl ester (10.0 g, 19.8 mmol) in a Parr pressure bottle in MeOH (69 mL) were added DMSO (62 mL) and triethylamine (21.8 mL, 157 mmol). To the reaction mixture were added palladium acetate (2.2 g, 9.1 mmol) and 1,3-bis (diphenylphosphino) propane (3.75g, 9.1 mmol). The mixture was shaken under 40 psi of CO at 70°C for 4 hours. The reaction mixture was cooled to room temperature and was diluted with diethyl ether (600 mL). The ether layer was washed with water (5 x 60 mL), dried (MgSO_4) and concentrated. The crude residue was purified by flash chromatography with hexanes/EtOAc (1:1) to afford 6.9 g (85% yield) of 4-[1-Benzyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-benzoic acid methyl ester. $^1\text{HNMR}$ (400 MHz, CDCl_3) δ 7.91 (d, 2H), 7.32 (d, 2H), 7.28-7.16 (comp, 6H), 6.82 (d, 1H), 6.79 (s, 1H), 6.68 (dd, 1H), 3.86 (s, 3H), 3.74 (s, 3H), 3.38 (s, 2H), 2.47-2.44 (comp, 8H); MS (M+1) 416.2.

E. 4-[1-Benzyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-N,N-diethyl-benzamide

To a solution of diethyl amine (1.88 mL, 18.2 mmol) in $\text{CH}_2\text{ClCH}_2\text{Cl}$ (7 mL) at room temperature was added a trimethylaluminum (9.1 mL, 18.2 mmol, 2M in hexanes) dropwise. The reaction mixture was stirred at room temperature for 1 hour. A solution of 4-[1-Benzyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-benzoic acid methyl ester (1.51 g, 3.64 mmol) in $(\text{CH}_2)_2\text{Cl}_2$ (6 mL) was added and the reaction mixture was heated to reflux for 14 hours. The solution was then cooled 0°C and sat. aqueous NaHCO_3 (15 mL) was added dropwise. The mixture was filtered through celite. The celite cake was washed with CH_2Cl_2 (40 mL). The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried (MgSO_4) and concentrated. The crude residue was purified by flash chromatography with EtOAc to afford 1.4 g (84% yield) of 4-[1-Benzyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-N,N-diethyl-benzamide. $^1\text{HNMR}$ (400 MHz, CDCl_3) δ 7.28-7.16 (comp, 10H), 6.84-6.80 (comp, 2H), 6.68 (dd, 1H), 3.74 (s, 3H), 3.52-3.48 (comp, 2H), 3.39 (s, 2H), 3.24-3.21 (comp, 2H), 2.47-2.42 (comp, 8H), 1.22-1.20 (comp, 3H), 1.19-1.16 (comp, 3H); MS (M+1) 457.2.

F. N,N-Diethyl-4-[4-(3-hydroxy-phenyl)-piperidin-4-yl]-benzamide

To a solution of 4-[1-Benzyl-4-(3-hydroxy-phenyl)-piperidin-4-yl]-N,N-diethyl-benzamide (1.11 g, 2.49 mmol) in acetic acid (8 mL) in a Parr pressure bottle was added

Pd(OH)₂ (10% on carbon, 0.4 g). The reaction mixture was shaken under 50 psi of H₂ for 20 hours. The reaction mixture was then filtered through celite. The celite cake was washed with EtOAc (250 mL) and the organic layer was concentrated to remove the acetic acid. The residue was partitioned between CH₂Cl₂ (10 mL) and 30% aqueous NH₄OH (10 mL). The organic layer was separated and the aqueous layer was washed with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried (MgSO₄) and concentrated to afford 0.74 g of N,N-Diethyl-4-[4-(3-hydroxy-phenyl)-piperidin-4-yl]-benzamide (83% yield) which was used with no further purification. ¹HNMR (400 MHz, CD₃CO₂D) δ 7.24-7.06 (comp, 5H), 6.75 (s, 1H), 6.70 (d, 1H), 6.58 (d, 1H), 3.49-3.40 (comp, 2H), 3.21-3.15 (comp, 2H), 2.90-2.85 (comp, 4H), 2.39-2.33 (comp, 4H), 1.20-1.15 (comp, 3H), 1.08-1.02 (comp, 3H); MS (M+1) 353.2.

The following compounds were made using the procedures set forth above in Example 1, starting with a compound analogous to the title compound of Example 1A wherein R³ is fluoro or methoxy, and adding the appropriate amine reactant in the procedure of Example 1E.

4-[1-Benzyl-4-(3-methoxy-4-methyl-phenyl)-piperidin-4-yl]-N,N-diethyl-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 7.01 (d, 1H), 6.68 (d, 1H), 6.61 (s, 1H), 3.70 (s, 3H), 3.41 (s, 2H), 2.18 (s, 3H); MS (M+1) 471.2.

4-[1-Benzyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-N-methyl-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 7.62 (d, 2H), 6.79 (d, 1H), 6.66 (d, 1H), 6.04 (br, 1H), 3.77 (s, 3H), 2.99 (d, 3H); MS (M+1) 415.2.

4-[1-Benzyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-2-fluoro-N,N-dimethyl-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 7.09 (d, 1H), 6.95 (d, 1H), 6.71 (d, 1H), 3.79 (s, 3H), 3.09 (s, 3H), 2.89 (s, 3H); MS (M+1) 447.2.

4-[1-Benzyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-N-ethyl-N-methyl-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 6.85-6.79 (comp, 2H), 6.68 (d, 1H), 3.79 (s, 3H), 3.4 (s, 2H), 3.1-2.82 (comp, 3H); MS (M+1) 443.3.

4-[1-Benzyl-4-(3-fluoro-phenyl)-piperidin-4-yl]-N,N-diethyl-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 7.02 (d, 1H), 6.88 (d, 1H), 6.81 (t, 1H), 2.62-2.22 (comp, 8H); MS (M+1) 445.2.

EXAMPLE 2

GENERAL PROCEDURE FOR REDUCTIVE ALKYLATION OF N,N-DIETHYL-4-[4-(3-HYDROXY, FLUORO OR METHOXY-PHENYL)-PIPERIDIN-4-YL]-BENZAMIDES

To a solution of N,N-Diethyl-4-[4-(3-hydroxy-phenyl)-piperidin-4-yl]-benzamide (1 equivalent) in CH₂Cl₂ (0.4M) was added the aldehyde (1.2 equivalents) followed by addition of acetic acid (1.2 equivalents) and NaBH(OAc)₃ (1.5 equivalents). The reaction mixture was

stirred at room temperature for 16 hours. The mixture was then partitioned between equal volumes of CH₂Cl₂ and sat. aqueous NaHCO₃. The organic layer was separated and the aqueous layer was washed with CH₂Cl₂ (3 x). The combined organic layers were dried (MgSO₄) and concentrated. Purification by flash chromatography afforded the desired tertiary amines in yields ranging from 60-95%.

The following compounds were made using the above procedure of Example 2, starting with a diarylsubstituted pyridine wherein R³ is fluoro or methoxy and R² is the appropriate amide group.

{4-[1-(3-Cyclohexyl-propyl)-4-(3-methoxy-phenyl)-piperidin-4-yl]-phenyl}-morpholin-4-yl-methanone. ¹HNMR (400 MHz, CDCl₃) δ 6.82 (d, 1H), 6.79 (s, 1H), 6.71 (d, 1H), 3.75 (s, 3H), 1.79-1.61 (comp, 8H); MS (M+1) 505.3.

{4-[1-Hexyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-phenyl}-morpholin-4-yl-methanone. ¹HNMR (400 MHz, CDCl₃) δ 6.81 (d, 1H), 6.79 (d, 1H), 6.68 (d, 1H), 3.75 (s, 3H), 1.46-1.41 (comp, 2H), 0.84 (t, 3H); MS (M+1) 465.3.

N,N-Diethyl-4-[4-(3-methoxy-phenyl)-1-(2-phenyl-propyl)-piperidin-4-yl]-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 6.82-6.79 (comp, 2H), 6.66 (d, 1H), 3.77 (s, 3H), 2.85 (m, 1H), 1.22 (d, 3H); MS (M+1) 485.3.

N,N-Diethyl-4-[1-hexyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 7.18 (t, 1H), 6.82-6.80 (comp, 2H), 6.67 (d, 1H), 3.74 (s, 3H), 3.57-3.42 (comp, 2H), 2.26-2.20 (comp, 2H), 0.84 (t, 3H); MS (M+1) 451.3.

4-[1-(3-Cyclohexyl-propyl)-4-(3-methoxy-phenyl)-piperidin-4-yl]-N,N-diethyl-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 6.81 (d, 1H), 6.76 (s, 1H), 6.68 (d, 1H), 3.73 (s, 3H), 3.23-3.19 (comp, 2H), 2.47-2.39 (comp, 2H); MS (M+1) 491.3.

4-[1-(3-Cyclohexyl-propyl)-4-(3-fluoro-phenyl)-piperidin-4-yl]-N,N-diethyl-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 7.01 (d, 1H), 6.86 (d, 1H), 6.82 (t, 1H), 3.59-3.4 (comp, 2H), 2.26-2.20 (comp, 2H); MS (M+1) 479.3

N,N-Diethyl-4-[4-(3-fluoro-phenyl)-1-(3-phenyl-propyl)-piperidin-4-yl]-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 7.02 (d, 1H), 6.69 (d, 1H), 6.81 (t, 1H), 3.33-3.19 (comp, 2H), 2.50 (t, 2H), 1.83-1.71 (comp, 2H); MS (M+1) 473.2.

N,N-Diethyl-4-[4-(3-fluoro-phenyl)-1-methyl-piperidin-4-yl]-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 7.02 (d, 1H), 6.85 (d, 1H), 2.61-2.41 (comp, 8H), 2.26 (s, 3H); MS (M+1) 369.2.

N,N-Diethyl-4-[4-(3-fluoro-phenyl)-1-hexyl-piperidin-4-yl]-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 7.02 (d, 1H), 6.92-6.80 (comp, 2H), 2.52-2.40 (comp, 2H), 1.63-1.45 (comp, 2H), 0.79 (t, 3H); MS (M+1) 439.3.

N,N-Diethyl-4-[4-(3-fluoro-phenyl)-1-(4-methyl-benzyl)-piperidin-4-yl]-benzamide.

¹HNMR (400 MHz, CDCl₃) δ 7.08 (d, 2H), 7.02 (d, 1H), 6.91 (d, 1H), 3.36 (s, 2H), 2.59-2.38 (comp, 8H), 2.31 (s, 3H); MS (M+1) 459.2.

N,N-Diethyl-4-[4-(3-fluoro-phenyl)-1-(2-methyl-pentyl)-piperidin-4-yl]-benzamide.

5 ¹HNMR (400 MHz, CDCl₃) δ 7.03 (d, 1H), 6.92 (d, 1H), 6.85 (t, 1H), 3.59-3.41 (comp, 2H), 1.75-1.59 (comp, 2H); MS (M+1) 439.3.

N,N-Diethyl-4-[4-(3-fluoro-phenyl)-1-(3-methyl-butyl)-piperidin-4-yl]-benzamide.

¹HNMR (400 MHz, CDCl₃) δ 7.02 (d, 1H), 6.93 (d, 1H), 6.83 (t, 1H), 3.31-3.19 (comp, 2H), 1.58-1.43- (m, 1H), 1.39-1.29 (comp, 2H), 0.86 (d, 6H); MS (M+1) 425.3.

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EXAMPLE 3**ALKYLATION OF N,N-DIETHYL-4-[4-(3-METHOXY-PHENYL)-PIPERIDIN-4-YL]-BENZAMIDE**

To a solution of N,N-Diethyl-4-[4-(3-methoxy-phenyl)-piperidin-4-yl]-benzamide (1 equivalent) in DMF (0.5M) was added K₂CO₃ (3-10 equivalents) and the alkyl or heteroaryl halide (1-5 equivalents). The reaction mixture was stirred at 60-120°C for 3-16 hours. The mixture was then cooled to room temperature and filtered. The filtrate was diluted with diethyl ether and the ether layer was washed with brine. The organic phase was dried (MgSO₄) and concentrated. Purification by flash chromatography afforded the desired amines in yields ranging from 30-85%.

15

The following compounds were made using a procedure analogous to that of Example 3, starting with the appropriate amide group.

4-[1-Allyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-N,N-diethyl-benzamide. ¹HNMR (400 MHz, CDCl₃) d 7.19 (t, 1H), 6.84-6.80 (comp, 2H), 6.69 (d, 1H), 5.88-5.79 (m, 1H), 5.15-5.10 (comp, 2H), 3.75 (s, 3H), 2.95-2.87 (comp, 2H); MS (M+1) 407.2.

20

4-[1-Cyclopropylmethyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-N,N-diethyl-benzamide. ¹HNMR (400 MHz, CDCl₃) d 7.18 (t, 1H), 6.85-6.79 (comp, 2H), 6.68 (d, 1H), 3.74 (s, 3H), 2.21-2.10 (comp, 2H), 1.88-1.78 (comp, 1H), 1.51-1.39 (comp, 2H); MS (M+1) 421.2.

N,N-Diethyl-4-[4-(3-methoxy-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]-benzamide. ¹HNMR (400 MHz, CDCl₃) d 8.15 (d, 1H), 7.44 (t, 1H), 6.88-6.84 (comp, 2H), 6.69 (d, 1H), 6.64 (d, 1H), 6.57 (t, 1H), 3.75 (s, 3H), 3.71-3.56 (comp, 4H), 2.58-2.40 (comp, 4H); MS (M+1) 444.4.

N,N-Diethyl-4-[4-(3-methoxy-phenyl)-1-pyrimidin-2-yl-piperidin-4-yl]-benzamide. ¹HNMR (400 MHz, CDCl₃) d 8.27 (d, 2H), 6.88-6.80 (comp, 2H), 6.68 (d, 1H), 6.44 (t, 1H), 3.95-3.75 (comp, 4H), 3.74 (s, 3H), 3.30-3.19 (comp, 2H); MS (M+1) 445.4.

35

EXAMPLE 4

DEPROTECTION OF METHYL ARYL ETHERS

To a solution of methyl ether (1 equivalent) in CH_2Cl_2 (0.4M) at -78°C was added a solution of boron tribromide (1-5 equivalents) in CH_2Cl_2 (1.0M) dropwise. The reaction mixture was stirred at -78°C for 1 hour was warmed to room temperature and stirred for an additional 4-6 hour. The mixture was quenched with slow addition of water and was brought to pH 8 with a saturated water/ NH_4OH solution. The aqueous layer was washed with CH_2Cl_2 . The organic phase was dried (MgSO_4) and concentrated. Purification by flash chromatography afforded the desired phenols in yields ranging from 60-95%.

Alternatively, the methyl ethers were deprotected with sodium hydride and ethane thiol in DMF as follows:

To a suspension of NaH (10 equivalents) in DMF (0.2M) at room temperature was added ethane thiol (10 equivalents) dropwise. The mixture was stirred for 5 minutes. To the reaction mixture was added a solution of the methyl ether (1 equivalent) in DMF (0.2M). The mixture was heated to 120°C for 10-16 hours. The reaction was cooled to room temperature and was quenched with water. The mixture was diluted with diethyl ether and the organic layer was washed with brine. The organic phase was dried (MgSO_4) and concentrated. Purification by flash chromatography afforded the desired phenols in yields ranging from 60-95%.

The following compounds were made using the procedure of Example 4.

N,N-Diethyl-4-[4-(3-hydroxy-phenyl)-1-methyl-piperidin-4-yl]-benzamide. $^1\text{HNMR}$ (400 MHz, CDCl_3) δ 6.72-6.67 (comp, 2H), 6.61 (d, 1H), 3.51-3.41 (comp, 2H), 2.24-3.19 (comp, 2H), 1.24 (s, 3H); MS (M+1) 367.1.

4-[1-Allyl-4-(3-hydroxy-phenyl)-piperidin-4-yl]-N,N-diethyl-benzamide. $^1\text{HNMR}$ (400 MHz, CDCl_3) δ 6.74-6.65 (comp, 2H), 6.64 (d, 1H), 5.99-5.80 (m, 1H), 5.22-5.15 (comp, 2H), 3.35-3.19 (comp, 2H), 3.05-2.95 (comp, 2H); MS (M+1) 393.2.

4-[1-Benzyl-4-(3-hydroxy-phenyl)-piperidin-4-yl]-N,N-diethyl-benzamide. $^1\text{HNMR}$ (400 MHz, CDCl_3) δ 6.78 (d, 1H), 6.63 (d, 1H), 6.61 (s, 1H), 3.50 (comp, 2H), 3.42 (s, 2H), 1.19-1.01 (comp, 3H); MS (M+1) 443.2.

4-[1-Cyclopropylmethyl-4-(3-hydroxy-phenyl)-piperidin-4-yl]-N,N-diethyl-benzamide. $^1\text{HNMR}$ (400 MHz, CDCl_3) δ 6.90 (s, 1H), 6.78-6.61 (comp, 2H), 3.30-3.19 (comp, 2H), 0.69-0.64 (comp, 2H), 0.33-0.30 (comp, 2H); MS (M+1) 407.2.

N,N-Diethyl-4-[4-(3-hydroxy-phenyl)-1-phenethyl-piperidin-4-yl]-benzamide. $^1\text{HNMR}$ (400 MHz, CDCl_3) δ 6.79 (d, 1H), 6.69 (s, 1H), 6.63 (d, 1H), 2.81-2.68 (comp, 2H); MS (M+1) 457.2

N,N-Diethyl-4-[4-(3-hydroxy-phenyl)-1-thiazol-2-ylmethyl-piperidin-4-yl]-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 7.69 (d, 1H), 7.27 (d, 1H), 7.09 (t, 1H), 6.77 (d, 1H), 6.68 (s, 1H), 6.59 (d, 1H), 3.75 (s, 2H); MS (M+1) 450.1.

N,N-Diethyl-4-[4-(3-hydroxy-phenyl)-1-thiophen-2-ylmethyl-piperidin-4-yl]-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 6.94-6.91 (comp, 2H), 6.78 (d, 1H), 6.64-6.60 (comp, 2H), 3.62 (s, 2H), 3.55-3.45 (comp, 2H); MS (M+1) 449.1.

N,N-Diethyl-4-[4-(3-hydroxy-phenyl)-1-(4-methyl-benzyl)-piperidin-4-yl]-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 6.98 (d, 2H), 6.79 (d, 1H), 6.62 (d, 1H), 6.46 (s, 1H), 3.32 (s, 3H), 2.29 (s, 3H); MS (M+1) 457.2.

10 **4-[1-Butyl-4-(3-hydroxy-phenyl)-piperidin-4-yl]-N,N-diethyl-benzamide.** ¹HNMR (400 MHz, CDCl₃) δ 6.74 (d, 1H), 6.66 (s, 1H), 6.61 (d, 1H), 1.48-1.39 (comp, 2H), 0.85 (t, 3H); MS (M+1) 409.3.

4-[1-(3-Cyclohexyl-propyl)-4-(3-hydroxy-phenyl)-piperidin-4-yl]-N,N-diethyl-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 6.78 (s, 1H), 6.72-6.66 (comp, 2H), 1.71-1.54 (comp 15 7 H), 0.83-0.72 (comp, 2H); MS (M+1) 477.3.

N,N-Diethyl-4-[1-hexyl-4-(3-hydroxy-phenyl)-piperidin-4-yl]-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 6.75 (d, 1H), 6.70 (s, 1H), 6.64 (d, 1H), 1.59-1.41 (comp, 2H), 0.84 (t, 3H); MS (M+1) 437.3.

N,N-Diethyl-4-[4-(3-hydroxy-phenyl)-1-(3-methyl-butyl)-piperidin-4-yl]-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 6.76 (s, 1H), 6.71 (d, 1H), 6.67 (d, 1H), 0.87 (d, 3H); MS (M+1) 423.3

N,N-Diethyl-4-[4-(3-hydroxy-phenyl)-1-isobutyl-piperidin-4-yl]-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 6.74 (d, 1H), 6.69 (s, 1H), 6.60 (d, 1H), 2.11-2.02 (comp, 2H), 1.80-1.73 (m, 1H), 0.86 (d, 6H); MS (M+1) 409.3.

25 **N,N-Diethyl-4-[4-(3-hydroxy-phenyl)-1-(4-isopropyl-benzyl)-piperidin-4-yl]-benzamide.** ¹HNMR (400 MHz, CDCl₃) δ 7.08 (t, 1H), 7.01 (d, 1H), 6.74 (d, 1H), 6.62 (d, 1H), 6.56 (s, 1H), 3.40 (s, 2H), 2.88-2.79 (m, 1H), 1.20 (d, 6H); MS (M+1) 485.3.

N,N-Diethyl-4-[4-(3-hydroxy-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl]-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 8.17-8.12 (m, 1H), 7.52-7.45 (m, 1H), 6.81-6.72 (comp, 2H), 6.66 (d, 1 H), 6.61-6.55 (comp, 2H), 3.70-3.42 (comp, 6H); MS (M+1) 430.4.

N,N-Diethyl-4-[4-(3-hydroxy-phenyl)-1-pyrimidin-2-yl-piperidin-4-yl]-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 8.27 (comp, 2 H), 6.57 (s, 1H), 6.44 (d, 1H), 3.91-3.85 (comp, 2H), 3.78-3.69 (comp, 2H), 3.51-3.47 (comp, 2H); MS (M+1) 431.3.

4-[1-Benzooxazol-2-yl-4-(3-hydroxy-phenyl)-piperidin-4-yl]-N,N-diethyl-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 7.34 (d, 1H), 7.02 (t, 1H), 6.81-7.74 (comp, 2H), 6.62 (dd, 1H), 3.81-3.71 (comp, 2H), 3.69-3.60 (comp, 2H); MS (M+1) 470.3.

4-[4-(3-Hydroxy-phenyl)-1-(4-methyl-benzyl)-piperidin-4-yl]-N,N-dimethyl-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 7.07 (d, 2H), 6.75 (d, 1H), 6.61 (d, 1H), 6.45 (s, 1H), 3.34 (s, 2H), 3.05 (s, 3H), 2.92 (s, 3H), 2.27 (s, 3H); MS (M+1) 429.3.

4-[4-(3-Hydroxy-phenyl)-1-(2-methyl-pentyl)-piperidin-4-yl]-N,N-dimethyl-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 7.09 (t, 1H), 6.76 (d, 1H), 6.68 (s, 1H), 3.07 (s, 3H), 1.1-0.98 (m, 1H), 0.88-0.82 (comp, 6); MS (M+1) 409.3.

4-[4-(3-Hydroxy-phenyl)-1-(3-methyl-butyl)-piperidin-4-yl]-N,N-dimethyl-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 7.20-7.05 (comp, 3H), 6.77 (s, 1H), 3.06 (s, 3H), 2.94 (s, 3H), 0.84 (d, 6H); MS (M+1) 395.3.

{4-[1-(4-Fluoro-benzyl)-4-(3-hydroxy-phenyl)-piperidin-4-yl]-phenyl}-piperidin-1-yl-methanone. ¹HNMR (400 MHz, CDCl₃) δ 6.96 (t, 2H), 6.78 (d, 1H), 6.61 (dd, 1H), 6.51 (s, 1H), 3.72-3.59 (comp, 2H), 3.36 (s, 2H), 3.35-3.31 (comp, 2H); MS (M+1) 473.2.

{4-[1-Hexyl-4-(3-hydroxy-phenyl)-piperidin-4-yl]-phenyl}-morpholin-4-yl-methanone. ¹HNMR (400 MHz, CDCl₃) δ 7.09 (t, 1H), 6.75 (d, 1H), 6.64 (s, 1H), 6.60 (d, 1H), 3.86-3.22 (comp, 8H), 0.83 (t, 3H); MS (M+1) 451.3.

EXAMPLE 5

20 TRIFLUORO-METHANESULFONIC ACID 3-[1-BENZYL-4-(4-DIETHYLCARBAMOYL-PHENYL)-PIPERIDIN-4-YL]-PHENYL ESTER

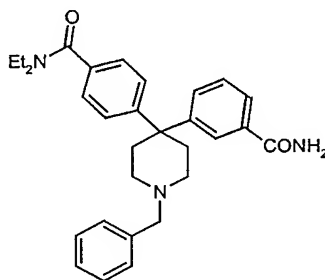
To a solution of 4-[1-Benzyl-4-(3-hydroxy-phenyl)-piperidin-4-yl]-N,N-diethyl-benzamide in CH₂Cl₂ (14 mL) at 0°C was added pyridine (0.43 mL, 5.33 mmol) followed by dropwise addition of triflic anhydride (0.9 mL, 5.33 mmol) over 5 minutes. The reaction mixture was stirred at 0°C for 1 hour and at room temperature for 2 hours. The solution was then cooled to 0°C and 15 mL of cold saturated aqueous NaHCO₃ were added. The organic layer was separated and the aqueous layer was washed with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried (MgSO₄) and concentrated. The crude residue was purified by flash chromatography with hexanes/EtOAc (4:1) to afford 1.57 g (77 % yield) of trifluoro-methanesulfonic acid 3-[1-benzyl-4-(4-diethylcarbamoyle-phenyl)-piperidin-4-yl]-phenyl ester. ¹HNMR (400 MHz, CDCl₃) δ 7.42-7.20 (comp, 11H), 7.15-7.02 (comp, 2H), 3.63-3.43 (comp, 2H), 3.42 (s, 2H), 3.35-3.29 (comp, 2H), 2.8-2.39 (comp, 8H), 1.31-1.21 (comp, 3H), 1.21-1.08 (comp, 3H); MS (M+1) 575.2.

EXAMPLE 6

35 4-[1-BENZYL-4-(3-CYANO-PHENYL)-PIPERIDIN-4-YL]-N,N-DIETHYL-BENZAMIDE

To a solution of trifluoro-methanesulfonic acid 3-[1-benzyl-4-(4-diethylcarbamoyl-phenyl)-piperidin-4-yl]-phenyl ester (1.82 g, 3.16 mmol) in DMF (14 mL) was added zinc cyanide (0.26 g, 2.21 mmol) and tetrakis triphenylphosphine palladium (0.73 g, 0.63 mmol). The reaction was stirred under a nitrogen atmosphere at 90°C for 5 hours. The mixture was cooled to room temperatures and it was diluted with diethyl ether (100 mL). The organic layer was washed with brine (5x 10 mL), dried (MgSO₄) and concentrated. Purification with hexanes/EtOAc (1:1) afforded 1.3 g (91% yield) of 4-[1-Benzyl-4-(3-cyano-phenyl)-piperidin-4-yl]-N,N-diethyl-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 7.69-7.20 (comp, 13H), 3.55-3.43 (comp, 2H), 3.41 (s, 2H), 3.31-3.19 (comp, 2H), 2.6-2.25 (comp, 8H), 1.28-1.19 (comp, 3H), 1.17-1.08 (comp, 3H); MS (M+1) 452.2.

EXAMPLE 7



4-[1-BENZYL-4-(3-CARBOXAMIDO-PHENYL)-PIPERIDIN-4-YL]-N,N-DIETHYL-BENZAMIDE

To a solution of 4-[1-Benzyl-4-(3-cyano-phenyl)-piperidin-4-yl]-N,N-diethyl-benzamide (0.11g, 0.24 mmol) in ethanol (0.3 mL) was added 3N aqueous Na₂CO₃ (0.6 mL) and 30% aqueous H₂O₂ (0.15mL). The reaction mixture was stirred at room temperature for 8 hours. The mixture was diluted with water (2 mL) and the aqueous layer was washed with CH₂Cl₂ (3x5 mL). The organic layer was dried (MgSO₄) and concentrated. The residue was purified by flash chromatography with CH₂Cl₂/MeOH (10:1) to afford 35 mg (31% yield) of 4-[1-Benzyl-4-(3-cyano-phenyl)-piperidin-4-yl]-N,N-diethyl-benzamide. ¹HNMR (400 MHz, CDCl₃) δ 7.79 (s, 1H), 7.55-7.20 (comp, 12H), 6.13 (br, 1H), 5.62 (br, 1H), 3.48-3.40 (comp, 2H), 3.38 (s, 2H), 3.23-3.19 (comp, 2H), 2.51-2.39 (comp, 8H), 1.27-1.20 (comp, 3H), 1.15-1.07 (comp, 3H); MS (M+1) 470.3.

EXAMPLE 8

1-BENZYL-4-(3-METHOXY-PHENYL)-4-(4-THIOPHEN-2-YL-PHENYL)-PIPERIDINE

To a solution of trifluoro-methanesulfonic acid 4-[1-benzyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-phenyl ester (0.1 g, 0.2 mmol) in ethanol (4.5 mL) and water (0.5 mL) was added 2-thiophene boronic acid (0.052 g, 0.5 mmol) and sodium carbonate (0.037 g, 0.29 mmol) and tetrakis triphenylphosphine palladium (0.02 g, 0.18 mmol). The reaction mixture

was heated to reflux for 2 hours. The mixture was then filtered and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography with hexanes/EtOAc (3:1) to afford 0.08 g (92% yield) of 1-Benzyl-4-(3-methoxy-phenyl)-4-(4-thiophen-2-yl-phenyl)-piperidine. ¹HNMR (400 MHz, CDCl₃) δ 7.50 (d, 2H), 7.33-7.18 (comp, 10 H), 7.07-7.00 (m, 1H), 6.89-6.63 (comp, 2H), 6.69 (d, 1H), 3.76 (s, 3H), 3.42 (s, 2H), 2.61-2.39 (comp, 8H); MS (M+1) 440.2.

The following compounds were made using a procedure analogous to that of Example 8, starting with the appropriate ester wherein R³ is methoxy, hydroxy or fluoro.

3-[1-Benzyl-4-(4-thiophen-2-yl-phenyl)-piperidin-4-yl]-phenol. ¹HNMR (400 MHz, CDCl₃) δ 7.46 (d, 2H), 7.16 (d, 2H), 6.80 (d, 1H), 6.59 (dd, 1H), 6.54 (s, 1H), 3.40 (s, 2H); MS (M+1) 426.0.

3-[1-Benzyl-4-(4'-trifluoromethyl-biphenyl-4-yl)-piperidin-4-yl]-phenol. ¹HNMR (400 MHz, CDCl₃) δ 7.67-7.58 (comp, 4H), 7.44 (d, 2H), 7.12 (t, 1H), 6.80 (d, 1H), 6.62-6.59 (comp, 2H); MS (M+1) 488.2.

3-[1-Benzyl-4-(4'-methyl-biphenyl-4-yl)-piperidin-4-yl]-phenol. ¹HNMR (400 MHz, CDCl₃) δ 7.45-7.40 (comp, 4H), 7.11 (t, 1H), 6.77 (d, 1H), 6.56 (s, 1H), 3.44 (s, 2H); MS (M+1) 434.3

3-[1-Benzyl-4-(3'-chloro-4'-fluoro-biphenyl-4-yl)-piperidin-4-yl]-phenol. ¹HNMR (400 MHz, CDCl₃) δ 7.54 (dd, 1H), 7.20-7.11 (comp, 2H), 6.80 (d, 1H), 6.65 (s, 1H), 6.62 (d, 1H), 3.44 (s, 2H); MS (M+1) 472.1.

EXAMPLES 9

4-[1-BENZYL-4-(3-METHOXY-PHENYL)-PIPERIDIN-4-YL]-BENZONITRILE

To a solution of trifluoro-methanesulfonic acid 4-[1-benzyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-phenyl ester (2.2 g, 4.34 mmol) in DMF (8 mL) was added zinc cyanide (0.61 g, 5.22 mmol) and tetrakis triphenylphosphine palladium (0.7 g, 0.63 mmol). The reaction was stirred under a nitrogen atmosphere at 90°C for 5 hours. The mixture was cooled to room temperature and it was diluted with diethyl ether (100 mL). The organic layer was washed with brine (5x 10 mL), dried (MgSO₄) and concentrated. Purification with hexanes/EtOAc (2:1) afforded 1.52 g (92% yield) of 4-[1-Benzyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-benzonitrile. ¹HNMR (400 MHz, CDCl₃) δ 7.51 (d, 2H), 7.34 (d, 2H), 7.28-7.18 (comp, 6 H), 6.80 (d, 1H), 6.77 (s, 1H), 6.70 (d, 1H), 3.75 (s, 3H), 3.39 (s, 2H), 2.63-2.39 (comp, 8H); MS (M+1) 383.2.

EXAMPLE 10

1-BENZYL-4-(3-METHOXY-PHENYL)-4-[4-(1H-TETRAZOL-5-YL)-PHENYL]-PIPERIDINE

To a solution of 4-[1-Benzyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-benzonitrile (0.24 g, 0.63 mmol) in toluene (5 mL) were added dibutyltin oxide (0.025 g, 0.1 mmol) and trimethylsilyl azide (0.15 g, 1.26 mmol). The reaction mixture was heated for 60 hours. The mixture was then cooled to room temperature and concentrated under vacuum. The residue was dissolved in methanol (5 mL) and then concentrated. The residue was partitioned between saturated aqueous sodium bicarbonate solution (5 mL) and ethyl acetate. The aqueous layer was washed with ethyl acetate (3x10 mL). The combined extracts were dried (MgSO₄) and concentrated. Purification by flash chromatography with CH₂Cl₂/MeOH (9:1) afforded 0.19 g (71% yield) of 1-Benzyl-4-(3-methoxy-phenyl)-4-[4-(1H-tetrazol-5-yl)-phenyl]-piperidine. ¹HNMR (400 MHz, CD₃OD) δ 7.95 (d, 2H), 7.44-7.41 (comp, 7H), 7.23-7.18 (m, 1H), 6.90-6.77 (comp, 2H), 6.76 (d, 1H), 6.70 (d, 1H), 4.21 (s, 2H), 3.64 (s, 3H), 3.30-2.41 (comp, 8H); MS (M+1) 426.2.

EXAMPLE 11

1-BENZYL-4-[4-(4,4-DIMETHYL-4,5-DIHYDRO-OXAZOL-2-YL)-PHENYL]-4-(3-METHOXY-PHENYL)-PIPERIDINE

To a solution of 4-[1-Benzyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-N-methyl-benzamide (1.01g, 2.44 mmol), in CH₂Cl₂ (24 mL) was added pyridine (0.30 mL, 3.71 mmol). The reaction was cooled to -50 °C and triflic anhydride (0.45, 2.67 mmol) was added dropwise over 1 minutes. The reaction was stirred at -50 °C for 1.5 hours and at room temperature for 0.5 hours. The mixture was cooled to -50 °C and 2-amino-2-methyl propanol (0.36 mL, 3.77 mmol) was added. The reaction was allowed to warm to room temperature and stirred at room temperature for 16 hours. To the mixture was added water (5 mL) and the aqueous layer was extracted with CH₂Cl₂ (3x15 mL). The combined extracts were dried (MgSO₄) and concentrated. Purification by flash chromatography with hexanes/EtOAc (1:1) afforded 0.75 g (68% yield) of 1-Benzyl-4-[4-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-phenyl]-4-(3-methoxy-phenyl)-piperidine. ¹HNMR (400 MHz, CDCl₃) δ; 7.83 (d, 2H), 7.38-7.21 (comp, 7H), 7.18 (t, 1H), 6.81-6.75 (comp, 2H), 6.63 (d, 1H), 4.08 (s, 2H), 3.78 (s, 3H), 3.41 (s, 2H), 2.79-2.40 (comp, 8H), 1.38 (s, 3H); MS (M+1) 454.2.

EXAMPLE 12

2-[4-[1-BENZYL-4-(3-METHOXY-PHENYL)-PIPERIDIN-4-YL]-PHENYL]-PROPAN-2-OL

To a solution of 4-[1-benzyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-benzoic acid methyl ester (3.3 g, 7.95 mmol) in THF (30 mL) at 0 °C was added methyl magnesium bromide (3M in diethyl ether, 10.6 mL, 31.8 mmol). The ice bath was removed and the reaction was stirred at room temperature for 5 hours and at 50 °C for 5 hours. The mixture was cooled to room temperature and was quenched with slow addition of water (15 mL). The aqueous layer was

washed with diethyl ether (3x 30 mL). The combined extracts were dried (MgSO₄) and concentrated. Purification by flash chromatography with hexanes/EtOAc afforded 3.1 g (94%) of 2-{4-[1-Benzyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-phenyl}-propan-2-ol. ¹HNMR (400 MHz, CDCl₃) δ 7.38-7.08 (comp, 10H), 6.81 (d, 1H), 6.61-6.59 (comp, 2H), 3.8 (s, 3H), 3.6 (s, 2H), 2.52-2.23 (comp, 8H), 1.42 (s, 6H); MS (M+1) 415.2.

The following compound was prepared by a procedure analogous to that of Example 12.

3-{4-[1-Benzyl-4-(3-fluoro-5-methoxy-phenyl)-piperidin-4-yl]-2-fluoro-phenyl}-pentan-3-ol. ¹HNMR (400 MHz, CDCl₃) δ 7.36 (d, 2H), 7.18 (d, 2H), 6.61 (s, 1H), 6.39 (d, 1H), 3.73 (s, 3H), 1.54 (s, 6H); MS (M+1) 434.0.

The following phenol derivatives were made using a procedure analogous to that of Example 12, followed by deprotection using the procedure of Example 4.

3-{1-(3-Cyclohexyl-propyl)-4-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-piperidin-4-yl}-phenol. ¹HNMR (400 MHz, CDCl₃) δ 6.74 (d, 1H), 6.63 (s, 1H), 6.58 (d, 1H), 2.21-2.18 (comp, 2H), 1.68-1.57 (comp, 4H), 0.82-0.79 (comp, 2H); MS (M+1) 436.3.

3-{1-Benzyl-4-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-piperidin-4-yl}-phenol. ¹HNMR (400 MHz, CDCl₃) δ 6.80 (d, 1H), 6.60-6.51 (comp, 2H), 3.39 (s, 2H), 2.55-2.18 (comp, 4H); MS (M+1) 402.2.

3-{1-Benzyl-4-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-piperidin-4-yl}-5-fluoro-phenol. ¹HNMR (400 MHz, CDCl₃) δ 7.06 (d, 2H), 6.46 (s, 1H), 6.42-6.30 (comp, 2H), 3.55 (s, 2H), 1.52 (s, 6H); MS (M+1) 420.1.

EXAMPLE 13

4-[1-BENZYL-4-(3-METHOXY-PHENYL)-PIPERIDIN-4-YL]-BENZOIC ACID HYDRAZIDE

To a solution of 4-[1-benzyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-benzoic acid methyl ester (9.5 g, 22.9 mmol) in methanol (60 mL) was added hydrazine hydrate (8 mL). The reaction mixture was heated to reflux for 36 hours. The mixture was cooled to room temperature and concentrated. The residue was dissolved in toluene (50 mL) and concentrated under vacuum, and 4-[1-Benzyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-benzoic acid hydrazide was obtained in quantitative yield. The residue was used in the subsequent steps without purification. ¹HNMR (400 MHz, CD₃OD) δ 7.82 (d, 1H), 7.67 (d, 1H), 7.39-7.05 (comp, 8H), 6.86 (d, 1H), 6.80 (s, 1H), 6.67 (d, 1H), 3.69 (s, 3H), 3.38 (s, 2H), 2.62-2.37 (comp, 8H); MS (M+1) 416.3.

EXAMPLE 14**CYCLOBUTANECARBOXYLIC ACID N'-(4-[1-BENZYL-4-(3-METHOXY-PHENYL)-
PIPERIDIN-4-YL]-BENZOYL)-HYDRAZIDE**

To a solution of 4-[1-Benzyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-benzoic acid
5 hydrazide (0.7 g, 1.69 mmol) in CH₂Cl₂ (10 mL) at 0°C was added triethylamine (0.35 mL, 2.5
mmol) was catalytic DMAP (20 mg) and cyclobutane carbonyl chloride (0.19 mL, 1.69 mmol).
The mixture was stirred at 0°C for 1 hour and at room temperature for 5 hours. The solution
was washed with brine (5 mL), dried (MgSO₄) and concentrated. Purification by flash
chromatography with hexanes/EtOAc (6:4) afforded 0.63 g (75% yield) of
10 cyclobutanecarboxylic acid N'-(4-[1-benzyl-4-(3-methoxy-phenyl)-piperidin-4-yl]-benzoyl)-
hydrazide. ¹HNMR (400 MHz, CDCl₃) δ 8.59 (s, 1H), 7.67 (d, 2H), 7.41-7.08 (comp, 8H), 6.82-
6.61 (comp, 3H), 3.79 (s, 3H), 2.41 (s, 2H), 3.09-3.02 (m, 1H), 2.41-2.23 (comp, 8H), 2.19-
1.67 (comp, 6H); MS (M+1) 498.2.

EXAMPLE 15**1-BENZYL-4-[4-(5-CYCLOBUTYL-[1,3,4]OXADIAZOL-2-YL)-PHENYL]-4-(3-METHOXY-
PHENYL)-PIPERIDINE**

To a solution of cyclobutanecarboxylic acid N'-(4-[1-benzyl-4-(3-methoxy-phenyl)-
piperidin-4-yl]-benzoyl)-hydrazide (0.2g, 0.40mmol) in CH₂Cl₂ (3 mL) was added pyridine
(0.08 mL, 1.0 mmol). The reaction mixture was cooled to -78°C. Triflic anhydride (0.14 mL,
20 0.84 mmol) was added dropwise. The mixture was stirred at -78°C for 1 hour and at room
temperature for 2 hours. The reaction was quenched with saturated aqueous sodium
bicarbonate (3 mL). The aqueous layer was washed with CH₂Cl₂ (3x 5mL) and the combined
extracts were dried (MgSO₄) and concentrated. Purification by flash chromatography with
EtOAc afforded 0.19 g (quantitative yield) of 1-Benzyl-4-[4-(5-cyclobutyl-[1,3,4]oxadiazol-2-yl)-
25 phenyl]-4-(3-methoxy-phenyl)-piperidine. ¹HNMR (400 MHz, CDCl₃) δ 7.92 (d, 2H), 7.37 (d,
2H), 7.36-7.16 (comp, 6H), 6.83 (d, 1H), 6.80 (s, 1H), 6.60 (d, 1H), 3.81-3.78 (m, 1H), 3.77 (s,
3H), 3.45 (s, 2H), 2.82-2.38 (comp, 10H), 2.21-2.19 (comp, 2H); MS (M+1) 480.2.

The following compound was made using a procedure analogous to that of Example
15.

30 **1-Benzyl-4-[4-(5-cyclopropyl-[1,3,4]oxadiazol-2-yl)-phenyl]-4-(3-methoxy-
phenyl)-piperidine.** ¹HNMR (400 MHz, CDCl₃) δ 7.92-7.81 (comp, 2H), 6.83 (d, 1H), 6.79 (s,
1H), 6.71-6.65 (m, 1H), 3.74 (s, 3H), 2.20-2.14 (m, 1H); MS (M+1) 466.4.

The following phenol derivatives were made using the procedure of Example 15,
followed by deprotection using the procedure of Example 4.

3-{1-Benzyl-4-[4-(5-methyl-[1,3,4]oxadiazol-2-yl)-phenyl]-piperidin-4-yl}-phenol.

¹HNMR (400 MHz, CDCl₃) δ 7.79 (d, 2H), 7.41-7.37 (comp, 2H), 7.12 (t, 1H), 3.63 (s, 2H), 2.57 (s, 3H); MS (M+1) 426.3.

3-{1-Benzyl-4-[4-(5-cyclopropyl-[1,3,4]oxadiazol-2-yl)-phenyl]-piperidin-4-yl}-

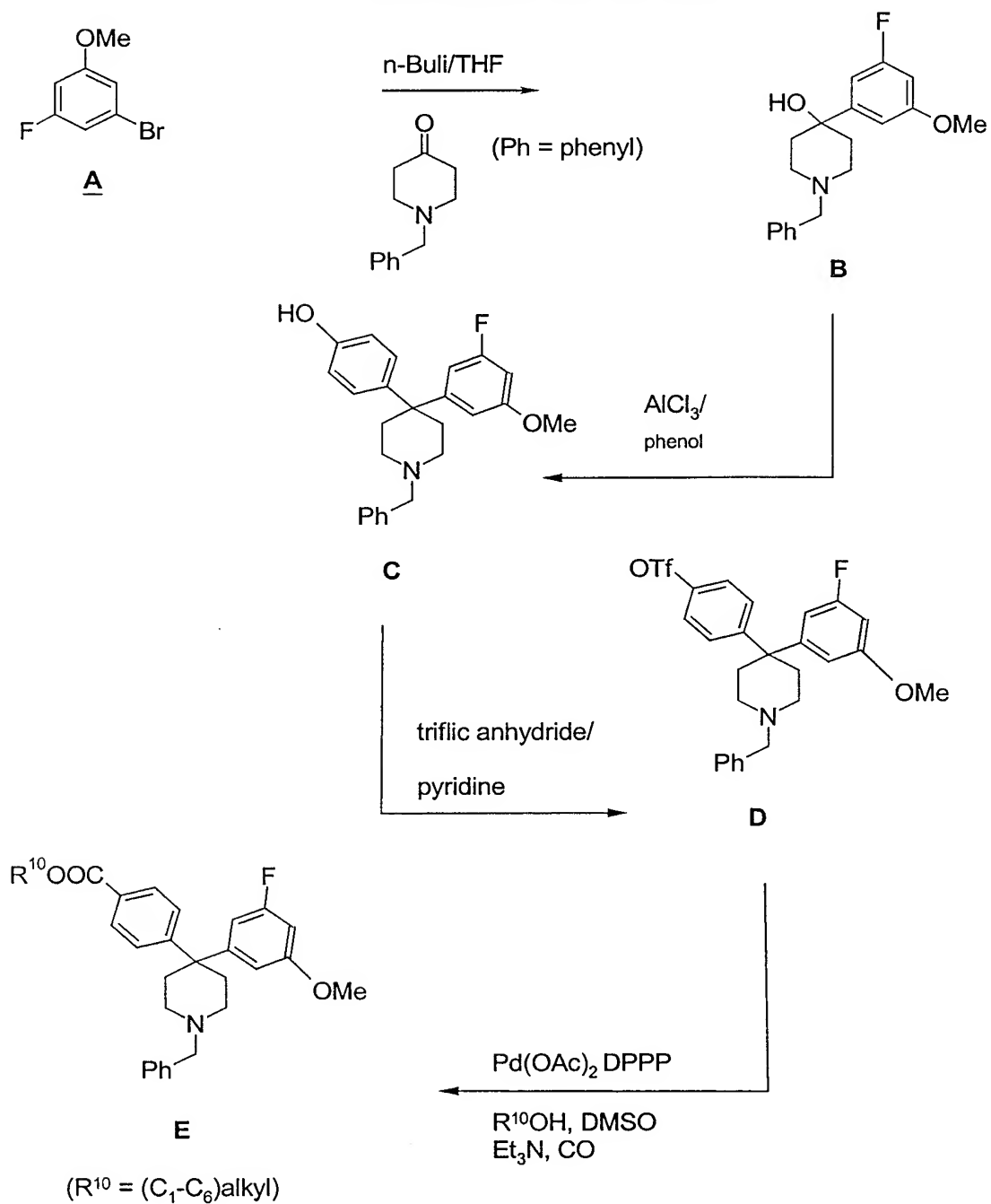
5 **phenol.** ¹HNMR (400 MHz, CDCl₃) δ 7.88-7.72 (comp, 2H), 7.56-7.42 (comp, 2H), 6.91-6.84 (m, 1H), 6.69-6.63 (m, 1H), 3.86 (s, 2H), 2.21-2.16 (m, 1H); MS (M+1) 452.2.

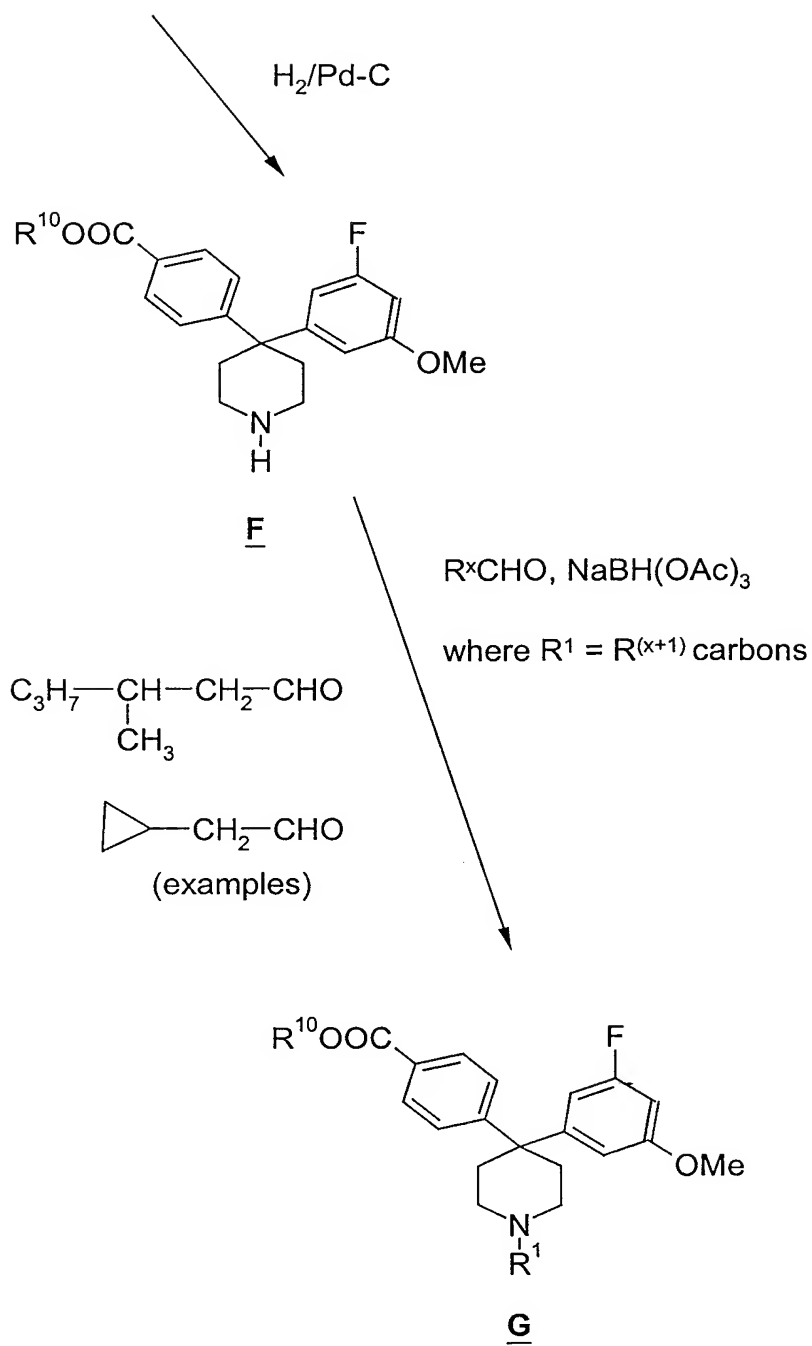
3-{1-Benzyl-4-[4-(5-ethyl-[1,3,4]oxadiazol-2-yl)-phenyl]-piperidin-4-yl}-phenol.

¹HNMR (400 MHz, CDCl₃) δ 7.79 (d, 2H), 7.11 (t, 1H), 7.75 (d, 1H), 6.65 (d, 1H), 6.55 (s, 1H), 2.90 (q, 2H), 1.38 (t, 3H); MS (M+1) 440.4.

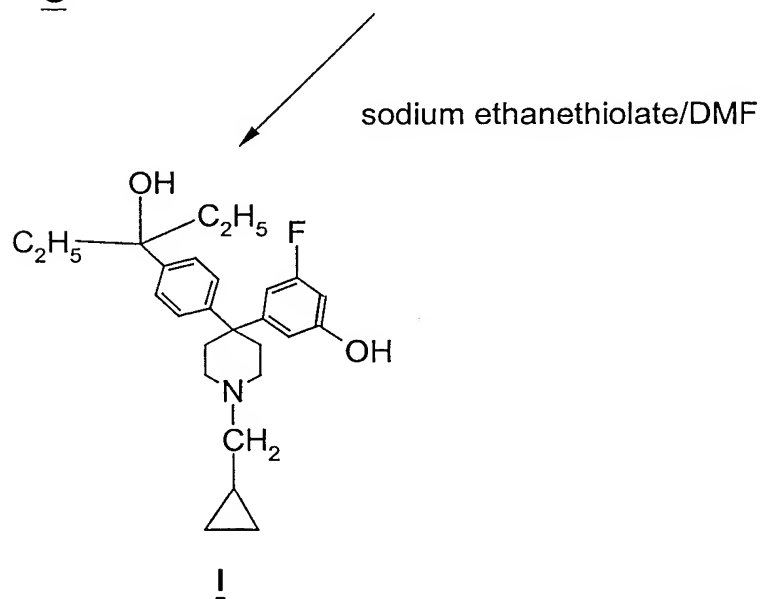
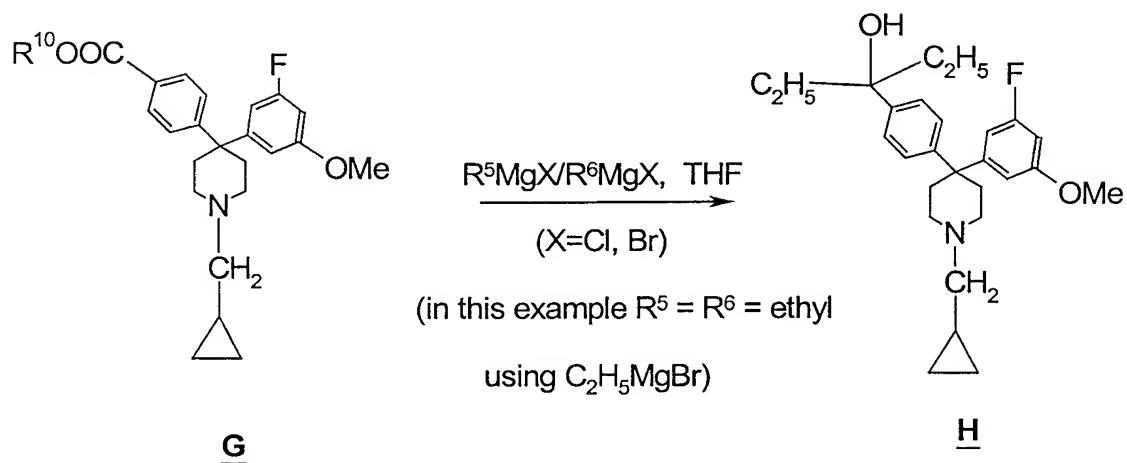
10 **3-{1-Benzyl-4-[4-(5-trifluoromethyl-[1,3,4]oxadiazol-2-yl)-phenyl]-piperidin-4-yl}-**

phenol. ¹HNMR (400 MHz, CDCl₃) δ 7.91 (d, 2H), 7.32 (d, 2H), 7.12 (t, 1H), 6.75 (d, 1H), 6.63-6.60 (comp, 2H), 3.42 (s, 2H); MS (M+1) 480.2.

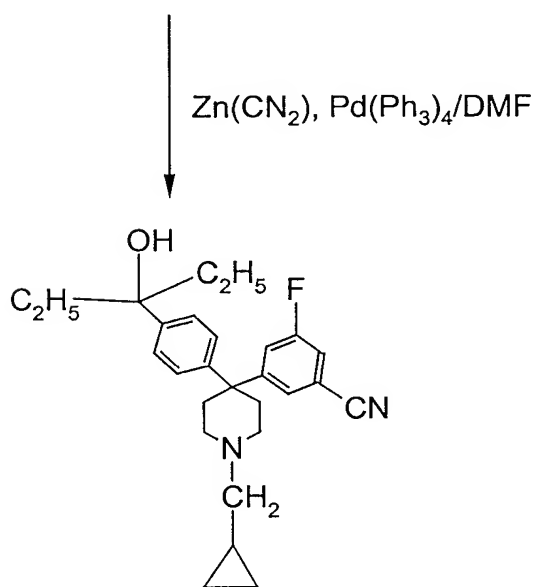
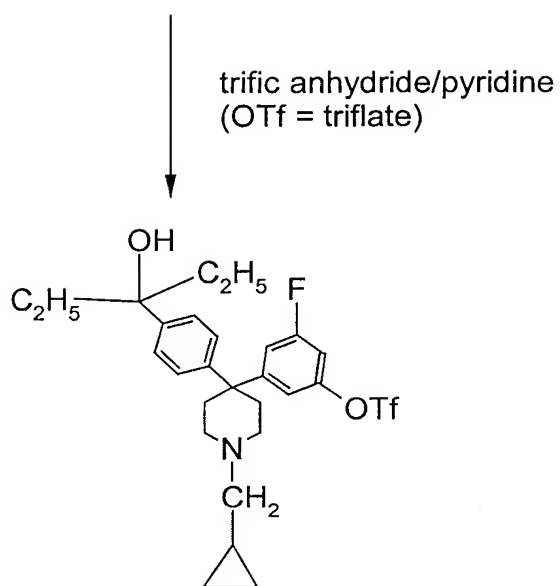
EXAMPLE 16**Additional synthetic pathways**



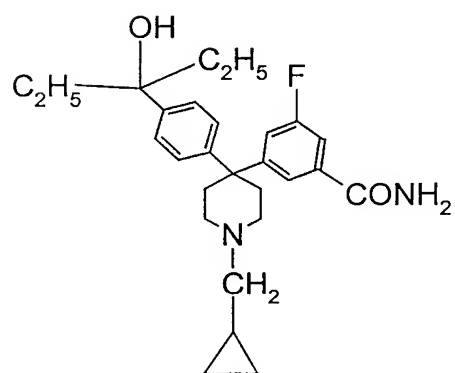
showing use of the cyclopentylmethyl group as R¹



(completed structure where R³ is OH, but for R³ = CONH₂ continue as below)



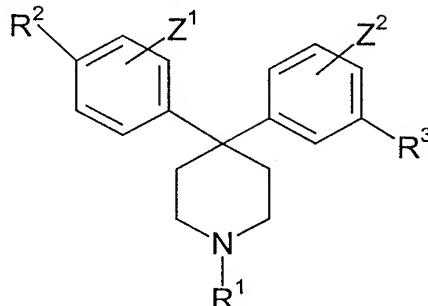
aq. $\text{H}_2\text{O}_2/\text{Na}_2\text{CO}_3$, ethanol



L

CLAIMS

1. A compound of the formula



I

- R¹ is hydrogen, (C₀-C₈)alkoxy-(C₀-C₈)alkyl-, wherein the total number of carbon atoms is eight or less, aryl, aryl-(C₁-C₈)alkyl-, heteroaryl, heteroaryl-(C₁-C₈)alkyl-, heterocyclic, heterocyclic-(C₁-C₈)alkyl, (C₃-C₇)cycloalkyl-, or (C₃-C₇)cycloalkyl-(C₁-C₈)alkyl, wherein said aryl and the aryl moiety of said aryl-(C₁-C₈)alkyl- are selected, independently, from phenyl and naphthyl, and wherein said heteroaryl and the heteroaryl moiety of said heteroaryl-(C₁-C₈)alkyl- are selected, independently, from pyrazinyl, benzofuranyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, isoindolyl, benzimidazolyl, purinyl, carbazolyl, 1,2,5-thiadiazolyl, quinazolinyl, pyridazinyl, pyrazinyl, cinnolyl, phthalazinyl, quinoxalinyl, xanthinyl, hypoxanthinyl, pteridyl, 5-azacytidinyl, 5-azauracil, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, oxazolyl, oxadiazoyl, isoxazolyl, thiazolyl, isothiazolyl, furanyl, pyrazolyl, pyrrolyl, tetrazolyl, triazolyl, thienyl, imidazolyl, pyridinyl, and pyrimidinyl; and wherein said heterocyclic and the heterocyclic moiety of said heterocyclic-(C₁-C₈)alkyl- are selected from saturated or unsaturated nonaromatic monocyclic or bicyclic ring systems, wherein said monocyclic ring systems contain from four to seven ring carbon atoms, from one to three of which may optionally be replaced with O, N or S, and wherein said bicyclic ring systems contain from seven to twelve ring carbon atoms, from one to four of which may optionally be replaced with O, N or S; and wherein any of the aryl, heteroaryl or heterocyclic moieties of R¹ may optionally be substituted with from one to three substituents, preferably with one or two substituents, independently selected from halo (i.e., chloro, fluoro, bromo or iodo), (C₁-C₆)alkyl optionally substituted with from one to seven (preferably with from zero to four) fluorine atoms, phenyl, benzyl, hydroxy, acetyl, amino, cyano, nitro, (C₁-C₆)alkoxy, (C₁-C₆)alkylamino and [(C₁-C₆)alkyl]₂amino, and wherein any of alkyl moieties in R¹ (e.g., the alkyl moieties of alkyl, alkoxy or alkylamino groups) may optionally be substituted with from one to seven (preferably with from zero to four) fluorine atoms;

R² is hydrogen, aryl, heteroaryl, heterocyclic, SO₂R⁴, COR⁴, CONR⁵R⁶, COOR⁴, or C(OH)R⁵R⁶ wherein each of R⁴, R⁵ and R⁶ is defined, independently, as R¹ is defined above,

or R⁵ and R⁶, together with the carbon or nitrogen to which they are both attached, form a three to seven membered saturated ring containing from zero to three heterocarbons selected, independently, from O, N and S, and wherein said aryl, heteroaryl, and heterocyclic are defined as such terms are defined above in the definition of R¹, and wherein any of the
5 aryl, heteroaryl and heterocyclic moieties of R² may optionally be substituted with from one to three substituents, preferably with one or two substituents, independently selected from halo (i.e., chloro, fluoro, bromo or iodo), (C₁-C₆)alkyl optionally substituted with from one to seven (preferably with from zero to four) fluorine atoms, phenyl, benzyl, hydroxy, acetyl, amino, cyano, nitro, (C₁-C₆)alkoxy optionally substituted with from one to seven (preferably with from zero to
10 four) fluorine atoms, (C₁-C₆)alkylamino and [(C₁-C₆)alkyl]₂amino;

R³ is hydroxy, NHSO₂R⁷, C(OH)R⁷R⁸, fluorine or CONHR⁷, wherein R⁷ and R⁸ are the same or different and are selected from hydrogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy and (C₁-C₄)alkoxy-(C₁-C₄)alkyl having a total of 4 or less carbon atoms, and wherein any of the alkyl moieties of R⁷ and R⁸ may optionally be substituted with from one to seven (preferably with
15 from zero to four) fluorine atoms; and

Z¹ and Z² are selected independently, from hydrogen, halo and (C₁-C₅)alkyl;

with the proviso that there are no two adjacent ring oxygen atoms and no ring oxygen atom adjacent to either a ring nitrogen atom or a ring sulfur atom in any of the heterocyclic or heteroaryl moieties of formula I;

20 or a pharmaceutically acceptable salt of such compound.

2. A compound according to claim 1 wherein R⁵ and R⁶ are selected, independently, from the groups set forth in the definition of R⁷ and R⁸.

3. A compound according to claim 1 wherein R¹ is cyclopropylmethyl, 3-cyclohexylpropyl, 2-phenylethyl, 2-methylpentyl, p-methylbenzyl, 2,2,2-trifluoroethyl, or 1-
25 methylpentyl.

4. A compound according to claim 2 wherein R¹ is cyclopropylmethyl, 3-cyclohexylpropyl, 2-phenylethyl, 2-methylpentyl, p-methylbenzyl, 2,2,2-trifluoroethyl, or 1-methylpentyl.

5. A compound according to claim 1 wherein R² is methyl ethyl amide, diethyl
30 amide, a diethyl carbinol, tetrazole, or pyrazole.

6. The compound according to claim 2 wherein R² is methyl ethyl amide, diethyl amide, a diethyl carbinol, tetrazole, or pyrazole.

7. A compound according to claim 1 wherein R³ is hydroxy, fluoro, CONH₂, NHSO₂CH₃, or methoxy.

8. A compound according to claim 2 wherein R³ is hydroxy, fluoro, CONH₂, NHSO₂CH₃, or methoxy.
35

9. A pharmaceutical composition for treating a disorder or condition selected from inflammatory diseases such as arthritis, psoriasis, asthma, or inflammatory bowel disease, disorders of respiratory function such as asthma, cough and apnea, allergies, gastrointestinal disorders such as gastritis, functional bowel disease, irritable bowel syndrome, functional diarrhoea, functional distension, functional pain, nonulcerogenic dyspepsia and other disorders of motility or secretion, and emesis, stroke, shock, brain edema, head trauma, spinal cord trauma, cerebral ischemia, cerebral deficits subsequent to cardiac bypass surgery and grafting, urogenital tract disorders such as urinary incontinence, chemical dependencies and addictions (e.g., addictions to or dependencies on alcohol, opiates, benzodiazepines, nicotine, heroin or cocaine), chronic pain, nonsomatic pain, acute pain and neurogenic pain, systemic lupus erythematosus, Hodgkin's disease, Sjogren's disease, epilepsy and rejection in organ transplants and skin grafts in a mammal, comprising an amount of a compound according to claim 1 that is effective in treating such disorder or condition and a pharmaceutically acceptable carrier.

10. A pharmaceutical composition for treating a disorder or condition, the treatment or prevention of which can be effected or facilitated by modulating binding to opioid receptors in a mammal, comprising an amount of a compound according to claim 1 that is effective in treating such disorder or condition and a pharmaceutically acceptable carrier.

11. A method for treating a disorder or condition selected from inflammatory diseases such as arthritis, psoriasis, asthma, or inflammatory bowel disease, disorders of respiratory function such as asthma, cough and apnea, allergies, gastrointestinal disorders such as gastritis, functional bowel disease, irritable bowel syndrome, functional diarrhoea, functional distension, functional pain, nonulcerogenic dyspepsia and other disorders of motility or secretion, and emesis, stroke, shock, brain edema, head trauma, spinal cord trauma, cerebral ischemia, cerebral deficits subsequent to cardiac bypass surgery and grafting, urogenital tract disorders such as urinary incontinence, chemical dependencies and addictions (e.g., addictions to or dependencies on alcohol, opiates, benzodiazepines, nicotine, heroin or cocaine), chronic pain, nonsomatic pain, acute pain and neurogenic pain, systemic lupus erythematosus, Hodgkin's disease, Sjogren's disease, epilepsy and rejection in organ transplants and skin grafts in a mammal, comprising administering to a mammal requiring such treatment an amount of a compound according to claim 1 that is effective in treating such disorder or condition.

12. A method for treating a disorder or condition, the treatment of which can be effected or facilitated by modulating binding to opioid receptors in a mammal, comprising administering to a mammal requiring such treatment an amount of a compound according to claim 1 that is effective in treating such disorder or condition.

13. A pharmaceutical composition for treating a disorder or condition selected from inflammatory diseases such as arthritis, psoriasis, asthma, or inflammatory bowel disease,

disorders of respiratory function such as asthma, cough and apnea, allergies, gastrointestinal disorders such as gastritis, functional bowel disease, irritable bowel syndrome, functional diarrhoea, functional distension, functional pain, nonulcerogenic dyspepsia and other disorders of motility or secretion, and emesis, stroke, shock, brain edema, head trauma, spinal cord trauma, cerebral ischemia, cerebral deficits subsequent to cardiac bypass surgery and grafting, urogenital tract disorders such as urinary incontinence, chemical dependencies and addictions (e.g., addictions to or dependencies on alcohol, opiates, benzodiazepines, nicotine, heroin or cocaine), chronic pain, nonsomatic pain, acute pain and neurogenic pain, systemic lupus erythematosus, Hodgkin's disease, Sjogren's disease, epilepsy and rejection in organ transplants and skin grafts in a mammal, comprising an opioid receptor binding modulating effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

14. A pharmaceutical composition for treating a disorder or condition, the treatment or prevention of which can be effected or facilitated by modulating binding to opioid receptors in a mammal, comprising an opioid receptor binding modulating effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

15. A method for treating a disorder or condition selected from inflammatory diseases such as arthritis, psoriasis, asthma, or inflammatory bowel disease, disorders of respiratory function such as asthma, cough and apnea, allergies, gastrointestinal disorders such as gastritis, functional bowel disease, irritable bowel syndrome, functional diarrhoea, functional distension, functional pain, nonulcerogenic dyspepsia and other disorders of motility or secretion, and emesis, stroke, shock, brain edema, head trauma, spinal cord trauma, cerebral ischemia, cerebral deficits subsequent to cardiac bypass surgery and grafting, urogenital tract disorders such as urinary incontinence, chemical dependencies and addictions (e.g., addictions to or dependencies on alcohol, opiates, benzodiazepines, nicotine, heroin or cocaine), chronic pain, nonsomatic pain, acute pain and neurogenic pain, systemic lupus erythematosus, Hodgkin's disease, Sjogren's disease, epilepsy and rejection in organ transplants and skin grafts in a mammal, comprising administering to a mammal requiring such treatment an opioid receptor binding modulating effective amount of a compound according to claim 1.

16. A method for treating a disorder or condition, the treatment or prevention of which can be effected or facilitated by modulating binding to opioid receptors in a mammal, comprising administering to a mammal requiring such treatment an opioid receptor binding modulating effective amount of a compound according to claim 1.

INTERNATIONAL SEARCH REPORT

International Application No
PC1/IB 99/01512

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D211/34 C07D211/22 A61K31/445 C07D401/04 C07D409/10
C07D401/10 C07D413/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | WO 96 31208 A (BYK GULDEN LOMBERG CHEM FAB ;KOLASSA NORBERT (DE); KORNUBER JOHAN) 10 October 1996 (1996-10-10) page 1 --- | 1,9-16 |
| A | CHEMICAL ABSTRACTS, vol. 98, no. 21, 23 May 1983 (1983-05-23) Columbus, Ohio, US; abstract no. 172575, NEUSER, DIETER ET AL: "The interactions of 1-alkyl-4,4-diphenylpiperidines with opiate receptors" XP002120659 abstract & EUR. J. PHARMACOL. (1983), 87(2-3), 315-18 , --- -/-- | 1,9-16 |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search

28 October 1999

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De Jong, B

INTERNATIONAL SEARCH REPORT

International Application No

PCI/IB 99/01512

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | WO 94 26712 A (FERRER INT ;FOQUET RAFAEL (ES); BOLOS JORDI (ES); SACRISTAN AURELI) 24 November 1994 (1994-11-24) --- | 1,9-16 |
| A | EP 0 657 428 A (LILLY CO ELI) 14 June 1995 (1995-06-14) ----- | 1,9-16 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 99/01512

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11, 12, 15, 16
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 11, 12, 15, 16
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compounds.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCI/IB 99/01512

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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| WO 9426712 A | 24-11-1994 | ES 2066721 A AU 675332 B AU 6928494 A CA 2140260 A EP 0651744 A FI 950197 A JP 7509255 T NO 950062 A NZ 267100 A ZA 9403036 A | 01-03-1995 30-01-1997 12-12-1994 24-11-1994 10-05-1995 17-01-1995 12-10-1995 06-01-1995 25-09-1996 02-05-1995 |
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